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Studies in Asymmetric Catalysis

by

Rina Soni

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Chemistry

University of Warwick, Department of Chemistry

September 2011

CONTENTS

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Declaration

The research described in this thesis is solely the work of the author unless otherwise stated. These studies were carried out at the Department of Chemistry, University of Warwick between October 2008 and September 2011. The content of this thesis has not been submitted, either wholly or partially for a degree at any other academic institution.

Some of this work has appeared in the scientific literature in the following publications:

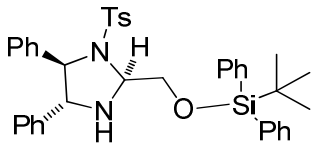
1) R. Soni, J. -M. Collinson, G. J. Clarkson, M. Wills. *Org. Lett.* **2011**, *13*, 4304-4307.

2) R. Soni, F. K. Cheung, G. J. Clarkson, J. E. D. Martins, M. A. Graham, M. Wills. *Org. Biomol. Chem.* **2011**, *9*, 3290-3294.

3) S. Gosiewska, R. Soni, G. J. Clarkson, M. Wills. *Tetrahedron Lett.* **2010**, *51*, 4214-4217.

Abstract

Derivatives of enantiomerically pure 1,2-cyclohexanediamine and 1,2-diphenylethanediamine have been synthesised and used as organocatalysts for asymmetric reactions. The derivatives of 1,2-diphenylethanediamine have been employed for C-C, C-N bond formation reactions to determine their efficacy and selectivity. Compound **278** has shown high efficiency and selectivity for addition of aldehydes to DEAD.



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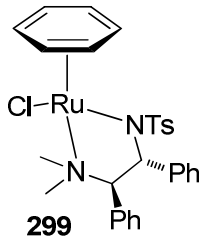

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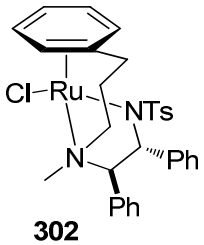


302

Novel Ru-metal complexes containing enantiomerically pure *N*,*N*-dialkylated-1,2-diamine ligands have been synthesised. Complexes **299** and **302** were used to study asymmetric transfer hydrogenation of ketones and imines. These complexes were found to be selective for the imine reduction compared to ketones reductions under the conditions used. Results obtained by these complexes also provided support for the proposal that reduction of the ketones involves a cyclic concerted mechanism for the transfer of hydrogen, while reduction of imines involves transfer of hydride from the complex through an 'open' transition state.

Asymmetric transfer hydrogenations of α,α-disubstituted ketones were carried out using Ru-3C-tethered catalyst **181**. Results obtained for asymmetric transfer hydrogenation of these compounds show that unsaturation or an aromatic group in substitution at the α-position of the ketone gave products of high enantioselectivity. This may be due to the interaction between η^6-arene ring of Ru-complex and the group placed on the α-position of the ketone.

List of Abbreviations

^{o}C	Degrees Celsius
δc	^{13}C-NMR chemical shift (ppm)
δ_H	^{1}H-NMR chemical shift (ppm)
δ_P	^{31}P-NMR chemical shift (ppm)
$[\alpha]_D$	Optical rotation
Å	Angstroms
Ac	Acetyl
AcOH	Acetic acid
aq	Aqueous
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
atm	Atmospheric pressure
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
br d	Broad doublet
br m	Broad multiplet
br s	Broad singlet
^{t}Bu	*tert*-Butyl
c	Concentration in grams per 100 cm^3
calcd	Calculated
CI	Chemical ionisation
COD	1,5-Cyclooctadiene
Compd.	Compound
Conf.	Configuration
Conv.	Conversion
Cp*	Pentamethylcyclopentadienyl
CYDN	1,2-Cyclohexanediamine
d	Doublet
dd	Doublet of doublets

DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
dec.	Decomposition temperature
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPEN	1,2-Diphenylethanediamine
dr	Diastereomeric ratio
dt	Doublet of triplets
DTAD	Di-*tert*-butyl azodicarboxylate
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalence
ESI	Electron spray ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FA	Formic acid
FA:TEA	Formic acid: triethylamine azeotrope (5:2)
FID	Flame ionisation detector
GC	Gas chromatography
h	Hours
HMB	Hexamethylbenzene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IPA	Isopropyl alcohol
inj.	Injection
J	Coupling constant (Hz)
m	Multiplet
M	Mol dm^{-3}
Me	Methyl
MeOH	Methanol

min.	Minutes
mp	Melting point
Ms	Mesyl
MTPA-Cl	α-Methoxy-α-trifluoromethylphenylacetyl chloride
MPV	Meerwein-Ponndorf-Verley reduction
NMR	Nuclear magnetic resonance
o-	*Ortho*
o/n	Overnight
p-	*Para*
Ph	Phenyl
PODPEN	1-Diphenylphosphinic-1,2-diphenylethanediamine
ppm	Parts per million
^{i}Pr	Isopropyl
PTC	Phase Transfer Catalyst
PTSA	*para*-Toluenesulfonic acid
PTsDPEN	Polyethylene glycol supported *N*-tosyl-1,2-diphenylethanediamine
q	Quartet
r.t.	Room temperature
s	Singlet
S/C	Substrate/Catalyst ratio
t	Triplet
t* or *tert	Tertiary
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAS	Tetrabutylammonium hydrogen sulfate
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethylamine
Temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ts	para-Toluenesulfonyl (Tosyl)
TsDPEN	*N*-Tosyl-1,2-diphenylethanediamine
UV	Ultraviolet
υ_{max}/cm^{-1}	Wave number (cm^{-1})

1 Introduction

1.1 Chirality

The term chirality is derived from the Greek word for hand (*Cheir*). In chemistry, chirality usually refers to molecules. A chiral molecule is a type of molecule that is non-superimposable on its mirror image. The two mirror images of chiral molecules are called enantiomers (optical isomers). Most commonly, chirality is created by the presence of an asymmetric carbon atom containing a bond to four different groups (Figure 1). Molecular chirality is of interest due to the importance of stereochemistry to different fields of chemistry. In a molecule, a chiral centre is also referred to as a stereocentre or stereogenic centre, leading to a spatial arrangement of attached ligands that result in non-superimposable mirror images.

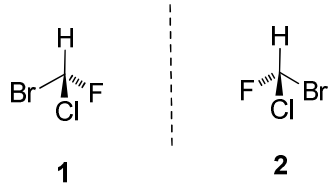


Figure 1: Determination of chirality in a molecule.

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence.[1] Thus, they have the same melting point, boiling point, solubility properties, retention time in chromatography, IR and NMR spectra as each other. They rotate the plane of polarised light in different directions, and for that reason enantiomers are sometimes referred to as optical isomers. The isomer which rotates the plane of light to the right is called the *dextro isomer* and is denoted as (+), while the other isomer will rotate the plane to the left in an equal amount and is known as the *levo isomer* denoted as (–).[2] Enantiomeric purity is reported as percentage enantiomeric excess (ee), which is calculated using equation ee = (*R*-

S)/(*R*+*S*) x 100. Enantiomeric purity can also be reported as enantiomeric ratio as *R*:*S*. In asymmetric synthesis, it is important to specify the enantiomeric purity and the absolute configuration at a given stereogenic centre (chiral centre).

The absolute configuration can be named by D/L or *R*/*S*. The D/L configuration can be identified by a relating molecule to glyceraldehyde and is mostly applied to carbohydrate and amino acid stereochemistry. Two isomers of glyceraldehyde are labelled as D and L. The absolute configuration R/S can be identified by using the Cahn-Ingold-Prelog system.[3] To determine the absolute configuration of a tetrahedral chiral centre, the four groups are first placed in the order of priority based on a series of priority rules. The tetrahedral centre is then viewed with the lowest priority group at the back, and the remaining three groups considered. If the groups lie in order of decreasing priority in clockwise direction it is denoted as the *R* (for *rectus*, Latin for right), and in the contrast if the groups are arranged in an anticlockwise direction it is denoted as the *S* (for *sinister*, Latin for left).[1,3]

1.1.1 Chirality in Nature

Chirality is an important factor in biological systems and in nature. Many natural compounds are chiral, including amino acids (the building blocks of proteins), sugars, and natural products. Out of the 21 natural amino acids, 20 have a stereogenic centre at the α-carbon, the one exception is glycine.[4] All natural amino acids are of the *L*-configuration, and the proteins formed by these building blocks are also chiral molecules. Proteins show high selectivity for the interaction with chiral molecules in a biological system.[5] Enzymes catalysing the chiral reactions show a preference for the one chiral product over the other. Enantiomers may have a

different test or smell, for example (*R*)-carvone smells like spearmint, while (*S*)-carvone smells like caraway (Figure 2).

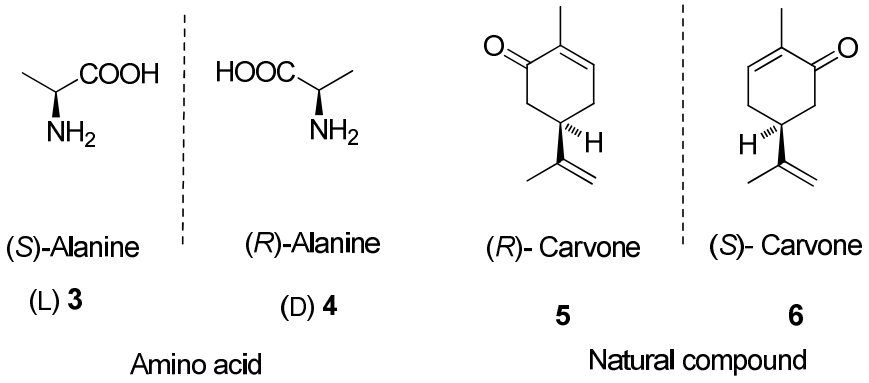


Figure 2: Chirality in nature.

1.1.2 Chirality in Pharmaceutical molecules

Nature has built its proteins only from *L* amino acids and therefore the biological systems of all living organisms exist in a chiral environment of single handedness. As a consequence, this is a major factor in the design of drug molecules.[6] When molecules are placed in chiral surroundings they actually behave very differently and this may lead to different effects. For example, the infamous thalidomide **7** (Figure 3) introduced in 1950s as a non-toxic sedative drug,[7] had antiemetic properties and was prescribed to pregnant women to counter morning sickness. The (*S*)-enantiomer had the desired antinausea effects, but the (*R*)-form was teratogenic and caused abnormalities in the child such as severely underdeveloped limbs. Even giving the pure (*S*)-enantiomer would not have prevented the tragedy. Unfortunately, the pure enantiomer of thalidomide racemises within 10 minutes in the bloodstream.[8] Thus use of the enantiomerically pure drug would not have prevented the devastating side effects and the drug was withdrawn from the market in 1961.

Another example is (–)-DOPA **8** used in the treatment of Parkinson's disease (Figure 3).[9] The active drug is an achiral compound dopamine, formed by the decarboxylation of **8**. But dopamine as such, is not able to cross the blood-brain barrier to reach the site of the action. If the compound given is racemic, the enzyme dopamine decarboxylase can only metabolise (–)-DOPA, but not (+)-DOPA. This would result in a dangerous build up of (+)-DOPA in the body, hence it is essential to administer DOPA as the pure (–) form.

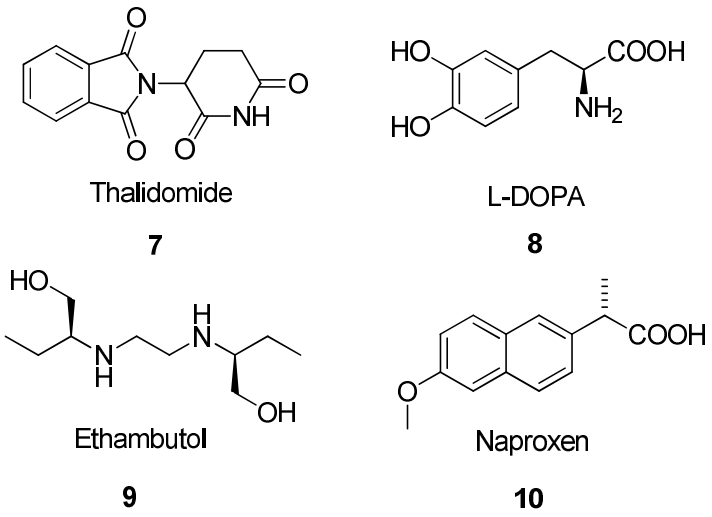


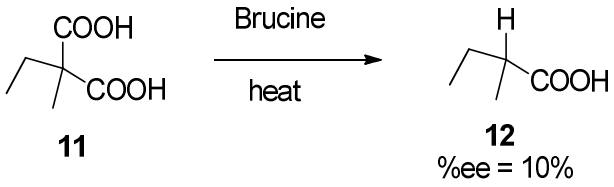
Figure 3: Chirality in pharmaceutical molecules.

Ethambutol **9** [(2*S*,2'*S*)-2,2'-(ethane-1,2-diyldiimino)dibutan-1-ol] is an antimycobacterial drug used against tuberculosis (Figure 3). It is usually given in combination with the other drugs such as rifampicin and pyrazinamide.[10] Naproxen **10**, as its sodium salt is a non-steroidal anti-inflammatory drug commonly used for the treatment of pain and stiffness in the case of osteoarthritis and gout diseases (Figure 3).[11]

1.2 Asymmetric synthesis

Asymmetric synthesis is organic synthesis which involves introduction of one or more elements of chirality. There are three different way to achieve an asymmetric synthesis: (1) chiral pool synthesis (2) chiral auxiliaries and (3) asymmetric catalysis.

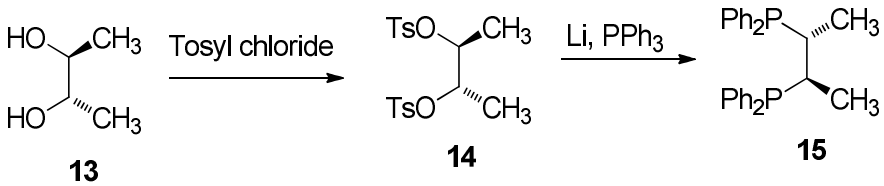
The oldest example for asymmetric synthesis was reported by Willy Marckwald in 1904.[12] The decarboxylation of 2-ethyl-2-methyl malonic acid mediated by brucine to give optically active 2-methyl butanoic acid with 10% ee (Scheme 1).



Scheme 1: Decarboxylation of 2-ethyl-2-methyl malonic acid.

1.2.1 Chiral pool synthesis

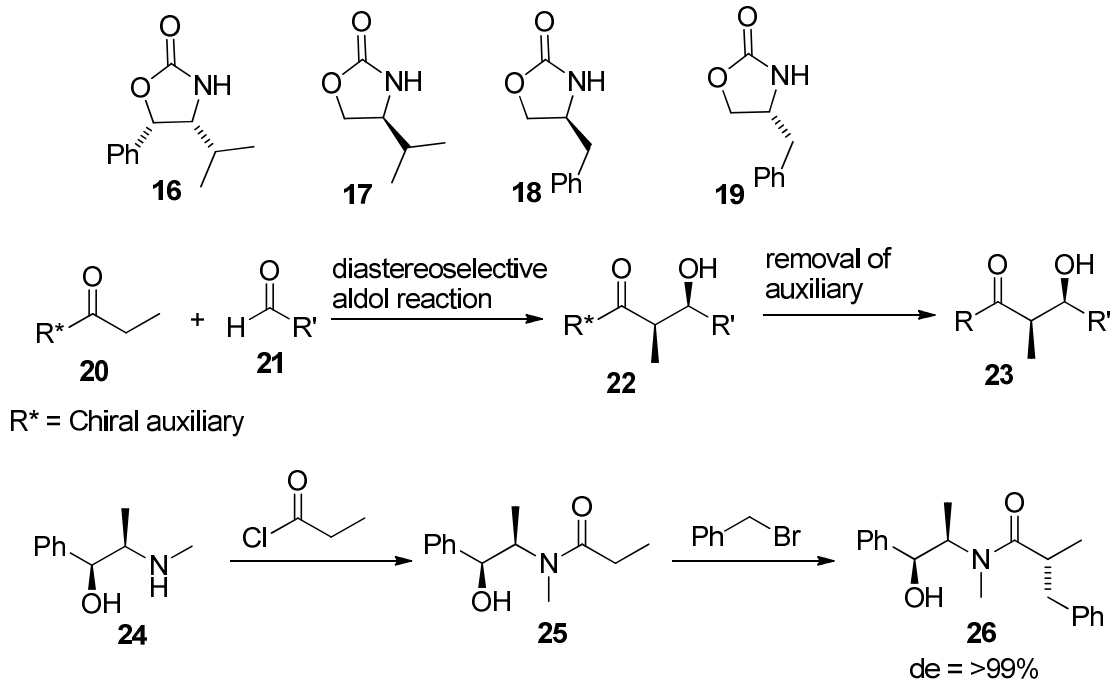
An enantiomerically pure starting compound (such as a sugar or amino acid) can be used for transformations that retain its chirality, which require stoichiometric amounts of the enantiopure starting material. For example, the enantiopure tartaric acid is used for the synthesis of chiraphos (Scheme 2).[13] Readily available (-)-pantolactone is used to synthesise part of epothilone, which is a new class of cancer drug.[14]



Scheme 2: Synthesis of Chiraphos.

1.2.2 Asymmetric induction

Enantiomers can be converted to diastereomers, i.e. an enantiopure reagent is used to create a second chiral centre, which is then removed as the desired product. The compounds used for such induction are called chiral auxiliaries such as Evans auxiliaries containing oxazolidinone groups or pseudoephedrine derivatives (Scheme 3). Evans chiral auxiliaries **16**-**19** can be used for the diastereoselective aldol reaction and after the reaction the auxiliary can be removed to give an enantiopure aldol product.[15] Pseudoephedrine **24** is converted to the amide, which can be reacted with an alkyl halide. The chiral auxiliary can be removed, for example by hydrolysis or by reduction to give an enantioselective product.[16]



Scheme 3: Asymmetric induction using chiral auxiliaries.[15-16]

1. 2.3 Asymmetric catalysis

A catalyst changes the rate of reaction without itself being consumed or transformed. Catalysis can be divided into homogenous catalysis (catalyst exists in the same phase

as the reaction mixture) and heterogeneous catalysis (catalyst act in different phase than the reaction mixture). In asymmetric catalysis, small amounts of a chiral catalyst are used to synthesise large amounts of enantiomerically pure molecules.[17]

There are different kinds of asymmetric catalysis including; (1) biocatalysis: involving the use of an enzyme (2) organometallic catalysis: involving the use of metal complexes (3) organocatalysis: involving the use of small organic molecules. All these asymmetric catalysis are widely used to form the enantiomerically pure compounds in small to large scale synthesis, as they have significant advantages over earlier methods of asymmetric synthesis which involve chiral resolution[18] or synthesis from enantiomerically pure starting compounds.

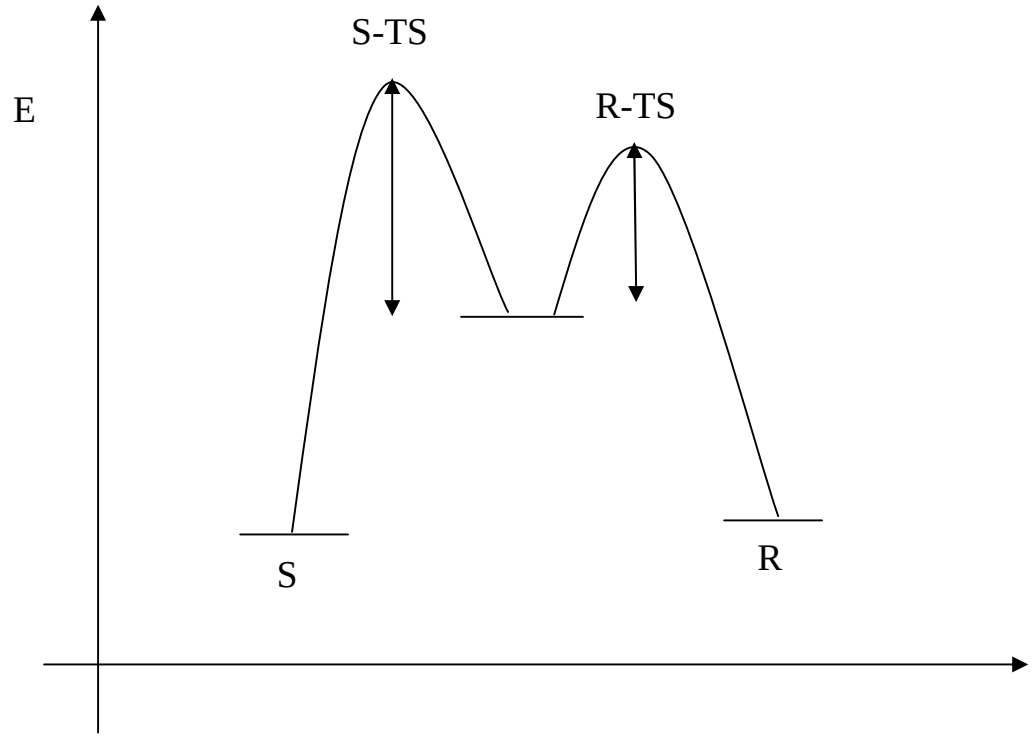


Figure 4: Chiral catalytic transition state.

In a standard laboratory synthesis, when achiral molecules undergo transformations to generate an asymmetric centre, a racemic product is obtained due to the reaction

following the same energetic pathway towards each enantiomer. The catalyst plays an important role in the rate of reaction by providing different transition states for the formation of each enantiomeric product and lowers the activation energy for the favoured product. The catalyst itself must be enantiomerically pure, in order to produce enantiomerically selective products *via* the energetically-preferred reaction through one of a pair of diastereomeric transition states (Figure 4).

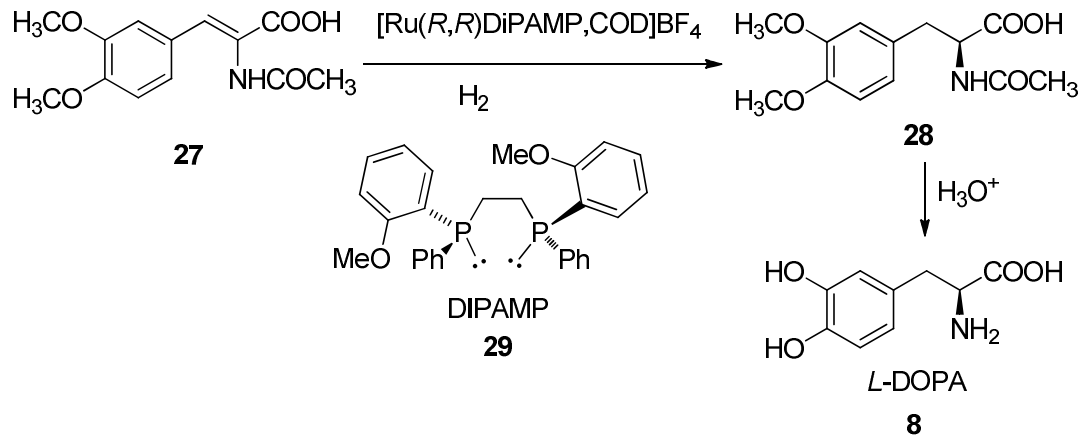
Although both *R* and *S* product enantiomers are identical in energy, the diastereomeric transition states leading to the *S* product is at a high energy level compared to that leading to the *R* product, and more energy is required to overcome this activation barrier. Therefore the formation of the *R* product would be more favourable, hence enantioselectivity is induced.[16] Thus, asymmetric catalysis reactions are very economical as very low mol% of catalysts may be required. Moreover in many reactions, the chiral ligands are often stable to the reaction conditions and may be recovered after use.

1. 2.3.1 Biocatalysts

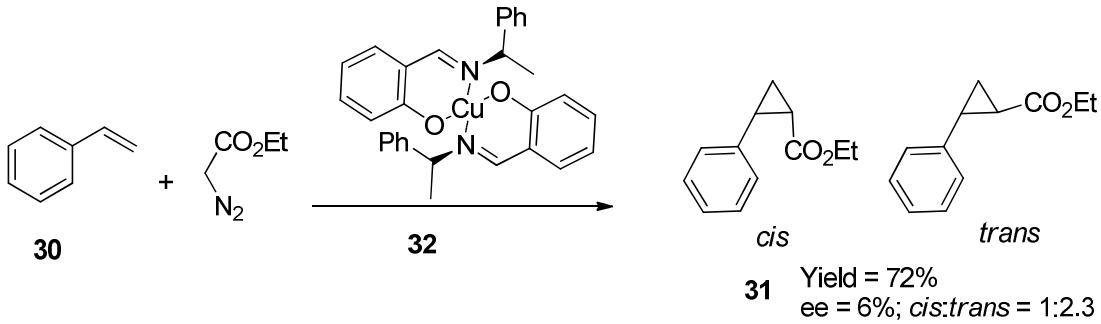
Enzymes are highly selective catalysts in the biological system with quite specific roles to play in different transformations. Isolated specific enzymes can be used as catalysts in organic synthesis for asymmetric reactions, due to the high inherent chirality present in them. But, enzyme catalysis has some draw backs such as lack of stability in organic solvents, extreme pH and high temperatures. Thus, the current level of use of enzymes in organic laboratories is quite low. Most enzymes have a limited scope with respect to their application in different reactions and to increase the scope of enzyme catalysis they must be modified *via* protein engineering.[19]

1. 2.3.2 Chiral ligand derived metal complexes

In asymmetric organometallic catalysis, organometallic complexes have been used as catalysts. Enantiopure organometallic complexes are usually obtained by combining enantiomerically pure ligands and a metal centre. The first practical example was asymmetric hydrogenation of alkenes using a Ru complex with enantiomerically pure diphosphine ligand DiPAMP developed in 1968 by William S. Knowles and used for the industrial production of *L*-DOPA (Scheme 4).[20]



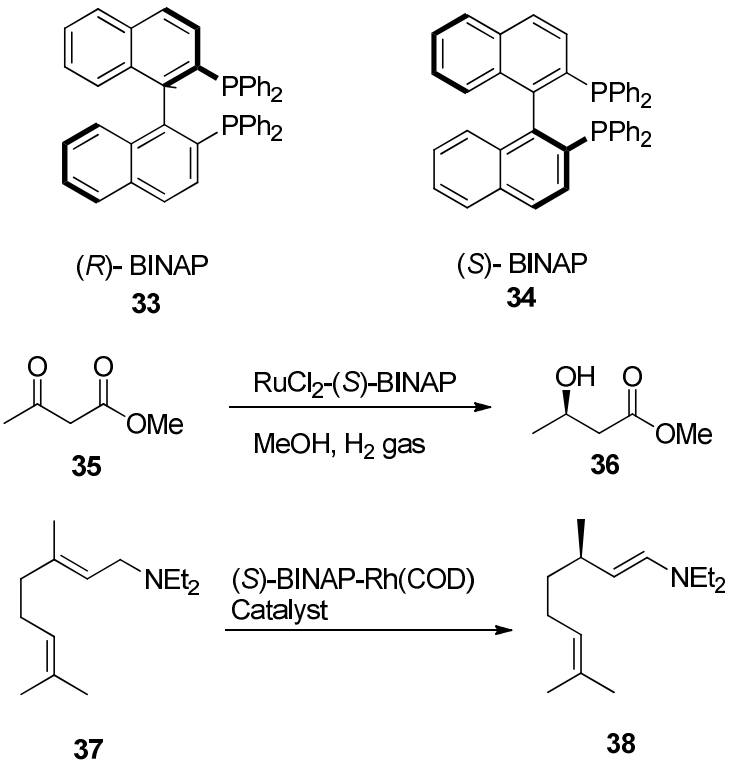
Scheme 4: Example of asymmetric organometallic catalysts for hydrogenation.



Scheme 5: Asymmetric cyclopropanation of styrene.

In the same year, Noyori reported the cyclopropanation of styrene using a chiral ligand, although for the first generation ligand the enantiomeric excess was very low

(Scheme 5).[21] Noyori has developed the chiral phosphine BINAP which can be used as an asymmetric hydrogenation catalyst in combination with Ru or Rh complexes.[22] Complexes of BINAP with Ru/Rh were found to be highly active for the enantioselective hydrogenation and isomerisation (Scheme 6). This process is used in the industrial synthesis of menthol using a chiral BINAP-Rh complex *via* asymmetric isomerisation of an allylic amine intermediate.[23]

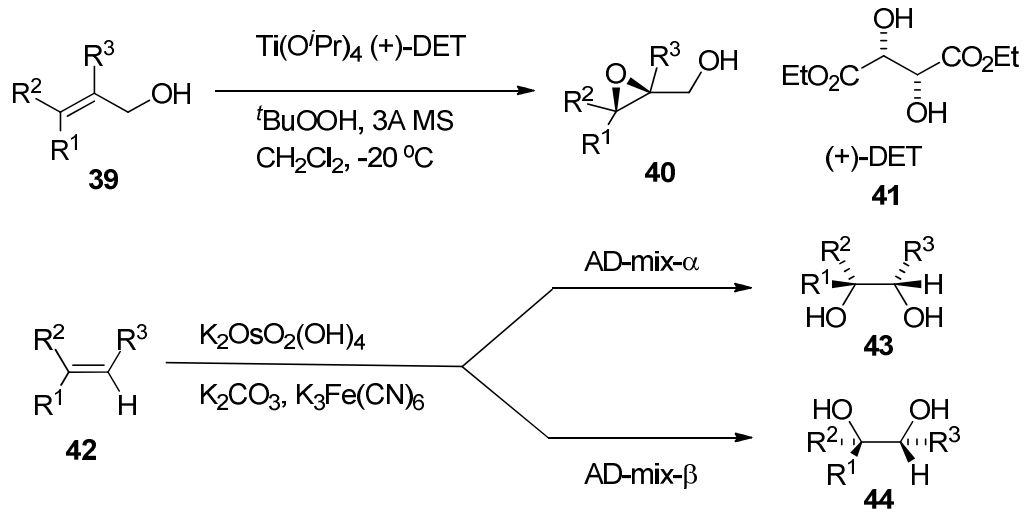


Scheme 6: Enantioselective hydrogenation and isomerisation using BINAP.

K. Barry Sharpless received the Nobel Prize in chemistry in 2001 along with William S. Knowles and Ryoji Noyori, for his work in enantioselective epoxidation[24] and enantioselective dihydroxylation[25]reactions (Scheme 7).

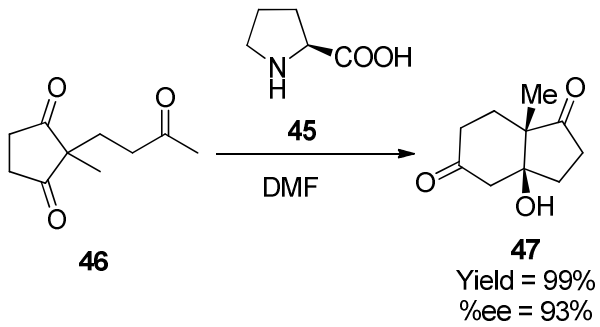
A number of organometallic complexes have been developed, studied and widely used for hydrogenation. Enantiomerically pure organometallic complexes comprising ruthenium, rhodium or iridium complexed with phosphine, amino

alcohol or diamine ligands have been found to be very efficient for asymmetric pressure hydrogenation and transfer hydrogenation of alkenes, carbonyl compounds and imines. As the resulting enantiopure products have important applications in the synthesis of enantiomerically pure biologically active molecules and natural products.



Scheme 7: Enantioselective epoxidation and dihydroxylation.

1.2.3.3 Chiral organocatalysts



Scheme 8: *L*-Proline catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction.

The first example of organocatalysis was the Doebner modification of the Knoevenagel condensation.[26] In the 1970s the reactions were developed by the teams

of Hoffmann-La Roche and Schering AG by using *L*-proline (**45**) as a catalyst for an intramolecular aldol reaction, which is now known as Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 8).[27-29]

A good chiral organocatalyst would be a small molecule, readily available in both enantiomeric forms, and easily separable from the product without racemization.[31] Chiral organic compounds which have been used to generate enantioselectivity in this way include (1) proline and its derivatives,[33-44] (2) primary amino acids and their derivatives[45-47] (3) cinchona alkaloids[48-50] and (4) imidazolidinone derivatives[51-63]. These catalysts were developed in earlier research because they are naturally available and easy to transform in different derivatives.

In organocatalysis, current research is mainly focused on use of chiral organocatalysts due to the number of applications and is referred asymmetric organocatalysis. Small molecules with multiple chiral centres can be synthesised using asymmetric organocatalysis to improve their selectivity towards biological targets. This can result in very potent and efficient biologically active compounds being prepared by short and efficient methods. In the synthesis of complex small molecules, the frequently used reactions are C-C, C-N, C-O, C-S and C-X (X = F, Cl, Br) bond-formation reactions. Asymmetric organocatalysis is now one of the fastest emerging fields in organic synthesis as well as in pharmaceutical chemistry.[31,32]

1.3 Asymmetric organocatalysis

Asymmetric organocatalysis is a developing area in the field of catalysis after enzyme- and organometallic catalysis. Asymmetric organocatalysis has a number of advantages over organometallic and enzyme catalysis such as more scope for

variations, ease of handling and low toxicity. For organocatalysts, conditions like inert atmosphere, low temperature or absolute solvents are not required. Organocatalysts are free from transition metals which gives them a wide scope for use in the synthesis of pharmaceutical and agricultural products.

1.3.1 Classifications

In the last few years, a number of research groups have developed novel organocatalysts for asymmetric transformations with high efficiency and selectivity. With the development of new organocatalysts, it has been revealed that they often exhibit different mechanisms and catalytic cycles. This has resulted in different ways to classifying organocatalysts.[64,65] The most versatile classification is enamine catalysis and iminium ion catalysis, depending on the intermediates formed in the catalytic cycle.

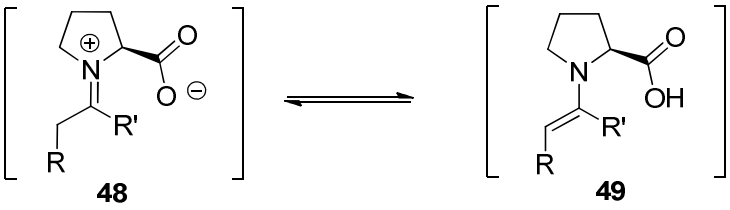


Figure 5: Iminium ion and Enamine intermediates.

In enamine catalysis the reaction proceeds *via* enamine intermediate formation by reaction of catalyst and substrate and also results in iminium ion formation at the end of the cycle. Iminium ion catalysis proceeds in the opposite way *via* an iminium ion formation by reaction of catalyst and substrate. Both enamine **49** and iminium ion **48** intermediates are interconvertable and complement each other (Figure 5).[33]

List, Barbas and Lerner published the first report on the enamine class of catalysts in an attempt to understand the reaction mechanism of the earlier reported Hajos-Parrish-Eder-Sauer-Wiechert reaction.[33] Following this, a number of reports were published for enamine catalysis using new catalysts with applications in different reactions such as the aldol reaction, Mannich reaction, Michael addition, α-amination, α-oxygenation, α-halogenations, α-sulphenylation, *etc*. Proline is most widely used in enamine catalysts. In recent years, several proline derivatives have been developed which exhibit high selectivity in the reactions which they catalyse (Figure 6).

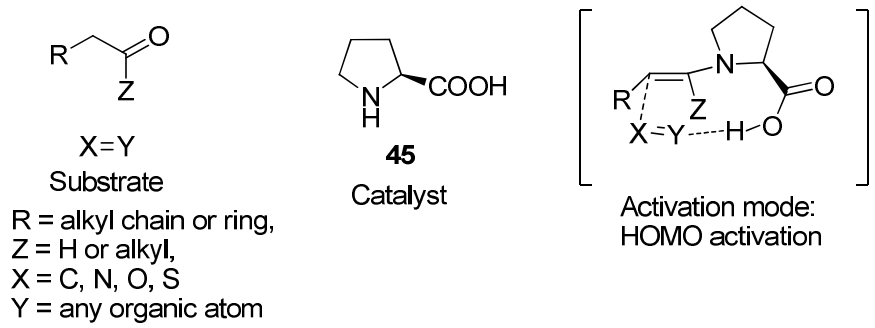


Figure 6: Enamine catalysis and their mode of activation.[59]

The first report on iminium ion catalysis was published by MacMillan and co-workers.[51] This has opened a new direction in organocatalysis. This class of catalysts forms an iminium ion intermediate with an unsaturated aldehyde (Figure 7). For this class of catalyst, detailed reaction mechanisms have been studied and published by MacMillan's group. This class of catalysts has been developed for a number of reactions including Diels-Alder reaction, Friedel-Crafts acylation, Mukaiyama-Michael addition, conjugate hydride reduction, conjugate amination, conjugate oxygenation, conjugate sulphenylation, epoxidation, *etc*.

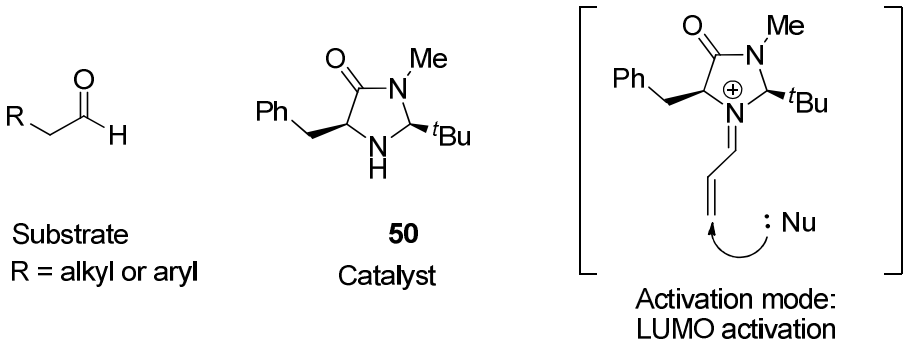


Figure 7: Iminium ion catalysis and their mode of activation.[59]

Earlier developed catalysts had a secondary or a primary amino group. In the last few years, a new class of organocatalysts has been developed as bifunctional catalysts. In this class, catalysts activate both substrate **51** and nucleophile **52** to give high efficiency and stereoselectivity (Figure 8). Bifunctional organocatalysts have been found to be very efficient for the Michael addition.[66]

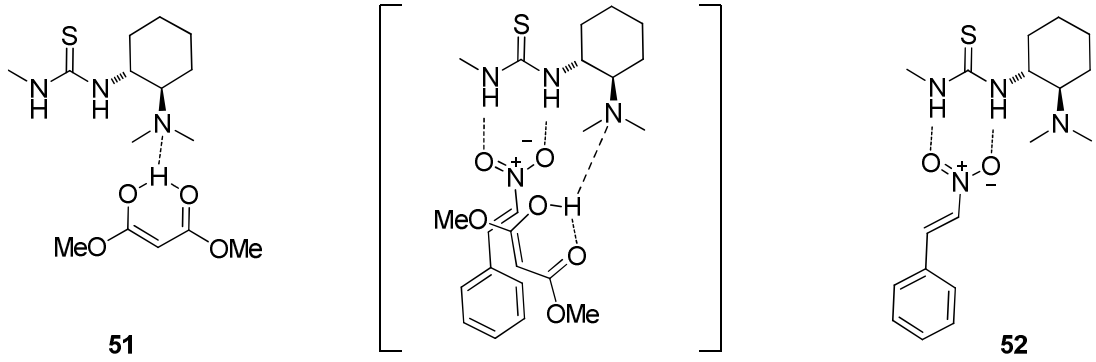


Figure 8: Bifunctional catalysts and their mode of activation.[66]

Organocatalysts which rely on acidic or basic properties may be classified into the following categories[64]: (1) Lewis Bases: these initiate the catalytic cycle *via* nucleophilic addition to substrate; (2) Lewis Acids: these activate nucleophilic substrates; (3) Brønsted Bases: the catalytic cycle is activated *via* deprotonation; (4) Brønsted Acids: the catalytic cycle is activated *via* protonation.

1.3.2 Different asymmetric reactions

In early work, proline and cinchona alkaloids were found to be promising as asymmetric organocatalysts. Various derivatives of both classes have been developed for different asymmetric reactions. In the last ten years, numbers of small organic molecules have also been found to be as efficient as asymmetric organocatalysts by different research groups. This has opened the new directions in asymmetric organocatalysis. Asymmetric organocatalysis has shown exponential growth in iminium-, enamine- and bifunctional based organocatalysis in reactions such as Michael additions, aldol reactions, Diels-Alder reaction, nucleophilic substitutions and many others.

1.3.2.1 Michael addition

Michael additions of ketones, aldehydes or 1,3-dicarbonyl compounds to nitroolefins, provide chiral nitroalkane derivatives.[67] These nitroalkane compounds are versatile intermediates in organic synthesis and can provide access to numbers of interesting compounds, as the nitro group can be converted into an amine,[68] nitrile oxide,[69] or hydrogen.[70] Several research groups are actively working on the development of enantioselective organocatalysts for the Michael reaction.[71-75] Recently several chiral derivatives have been developed for the Michael addition of ketone or aldehyde to nitroolefins with a few representative examples as shown in Figure 9.[76-83] Similarly selected examples are shown in Figure 10 for Michael addition of 1,3-dicarbonyl compound to nitroolefins in high efficiency and selectivity.[71,73, 84-87]

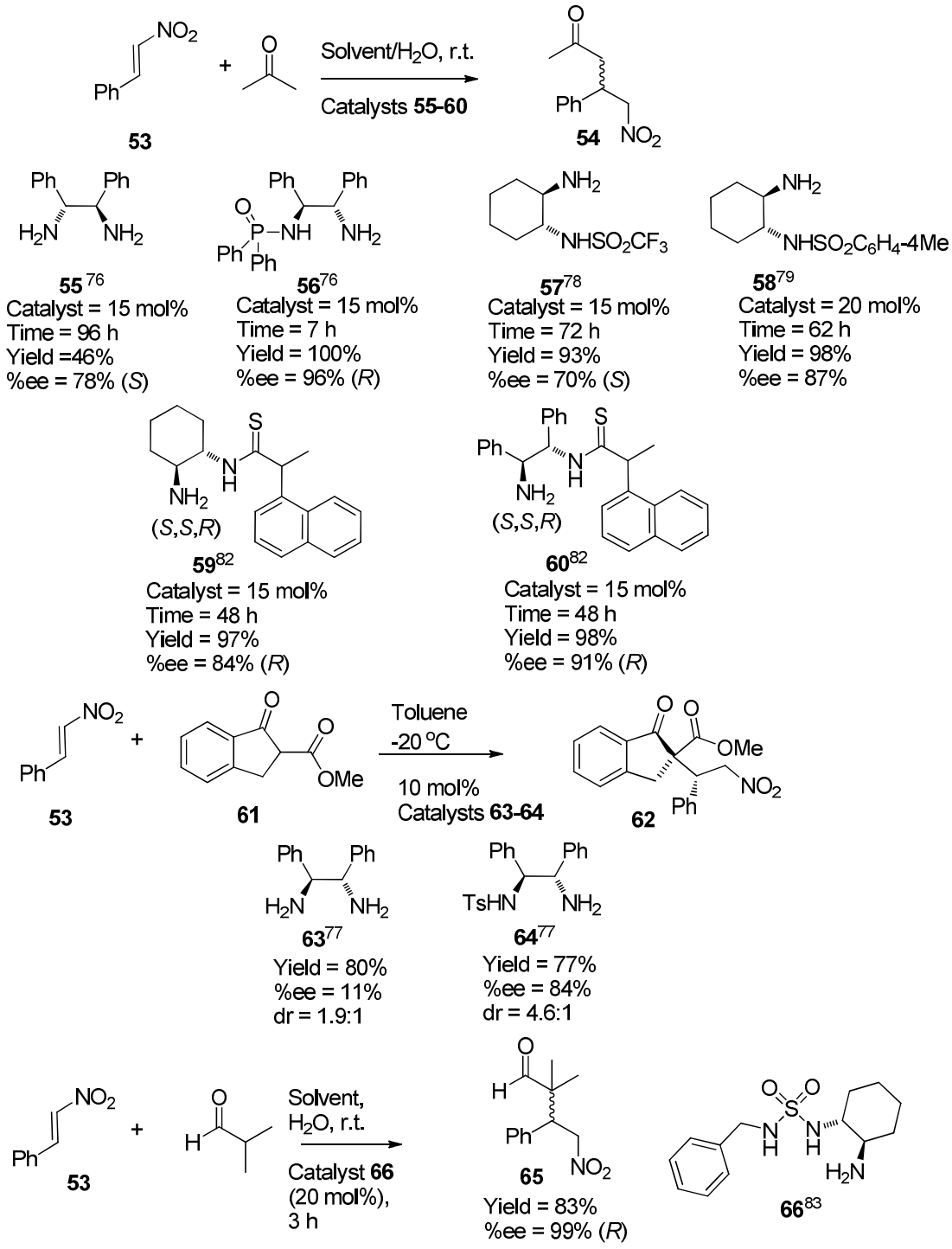


Figure 9: Asymmetric organocatalysts for the Michael addition of ketone or aldehyde to nitroolefins.

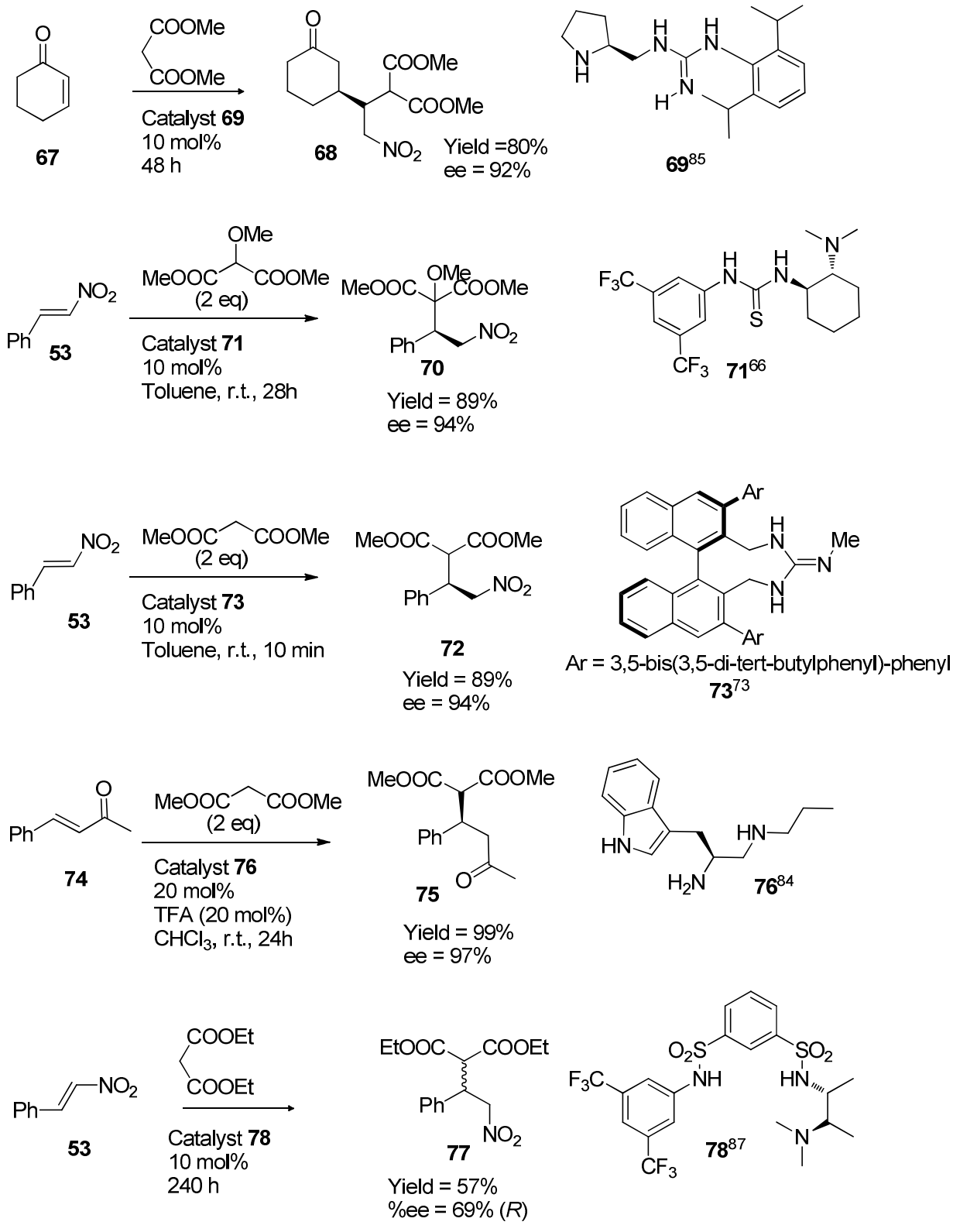


Figure 10: Asymmetric organocatalysts for the Michael addition of 1,3-dicarbonyl derivatives to nitroolefins/unsaturated ketones.

1.3.2.2 Aldol reaction

Asymmetric aldol reactions are useful for the α-functionalization of aldehydes and ketones. These compounds can be used as very good building blocks for small heterocyclic compounds, hydroxy derivatives and in carbohydrate chemistry.

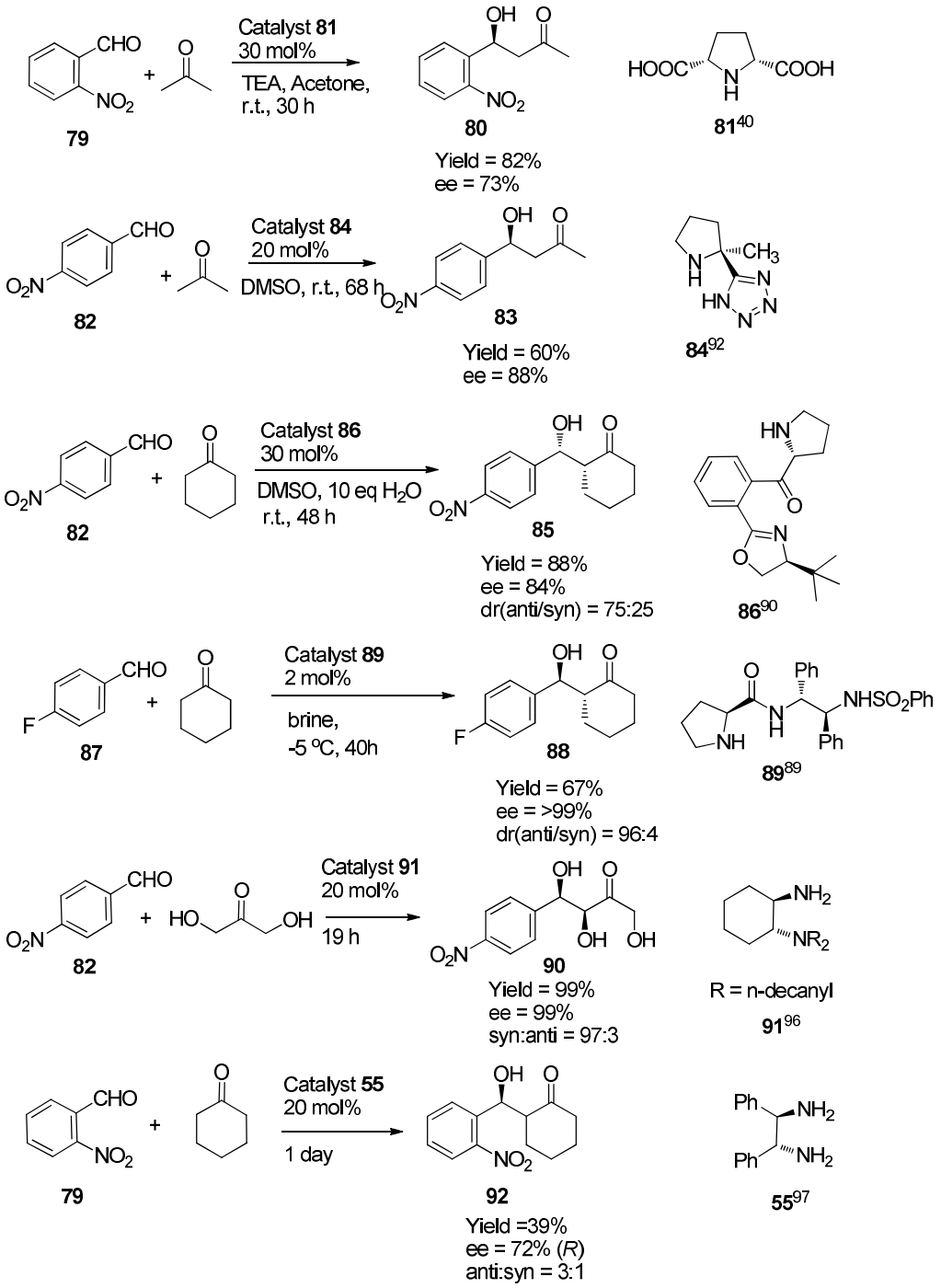


Figure 11: Asymmetric organocatalysts for the aldol reaction.

Moreover, β-hydroxy carbonyl derivatives are formed by aldol reactions, which are very useful derivatives for natural products and even in medicinal chemistry.[88] Due to this huge demand, several groups are working on asymmetric aldol reaction using organocatalysts.[52,89-95] Recently, various asymmetric organocatalysts have been found to be good for the aldol reaction (Figure 11).[40, 96-97]

The mechanism of an aldol reaction is illustrated in Figure 12 with an amine-based organocatalyst. In the catalytic cycle the tautomerization of the imine form **93** into the enamine form **94** is essential. Moreover, the enamine **93** has an extra N-H for organocatalysts such as primary amine or amino acid, which may control the structure of the enamine and direct the reaction to occur with enantioselectivity.[98]

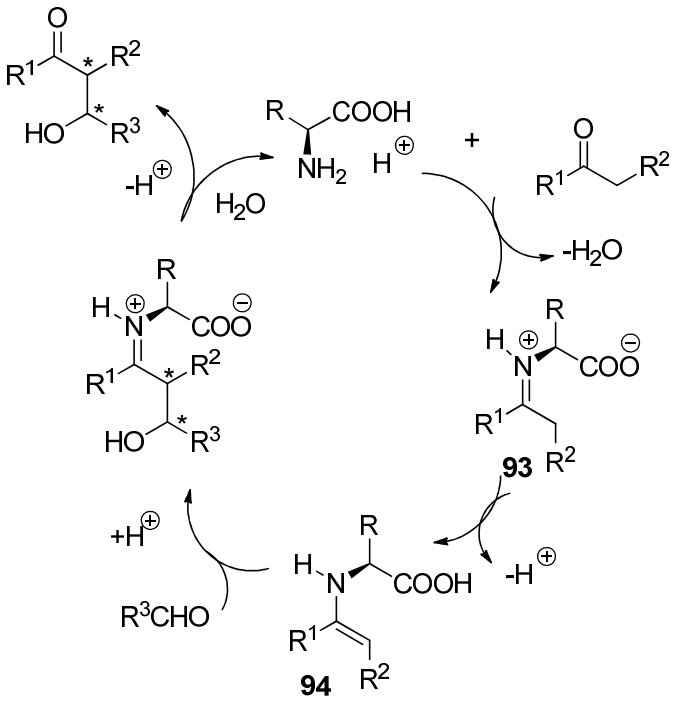


Figure 12: Mechanism of the aldol reaction using organocatalysts.[98]

1.3.2.3 Henry reaction

The Henry (nitroaldol) reaction is a good and quite economical C-C bond forming reaction. This reaction allows a stereogenic centre to be generated at the β-position of nitro functionality. The resulting β-nitro alcohol products can be converted in to α-hydroxy ketones. Both these products are very useful as chiral building block for natural products. Due to the recent development of asymmetric organocatalysis, research groups have focused on asymmetric versions of the Henry reaction. Earlier, different metal complexes have been combined with different chiral ligands.[99] Recently, chiral ligands with Cu salts have been found to be very promising for asymmetric Henry reactions (Figure 13).[100-101]

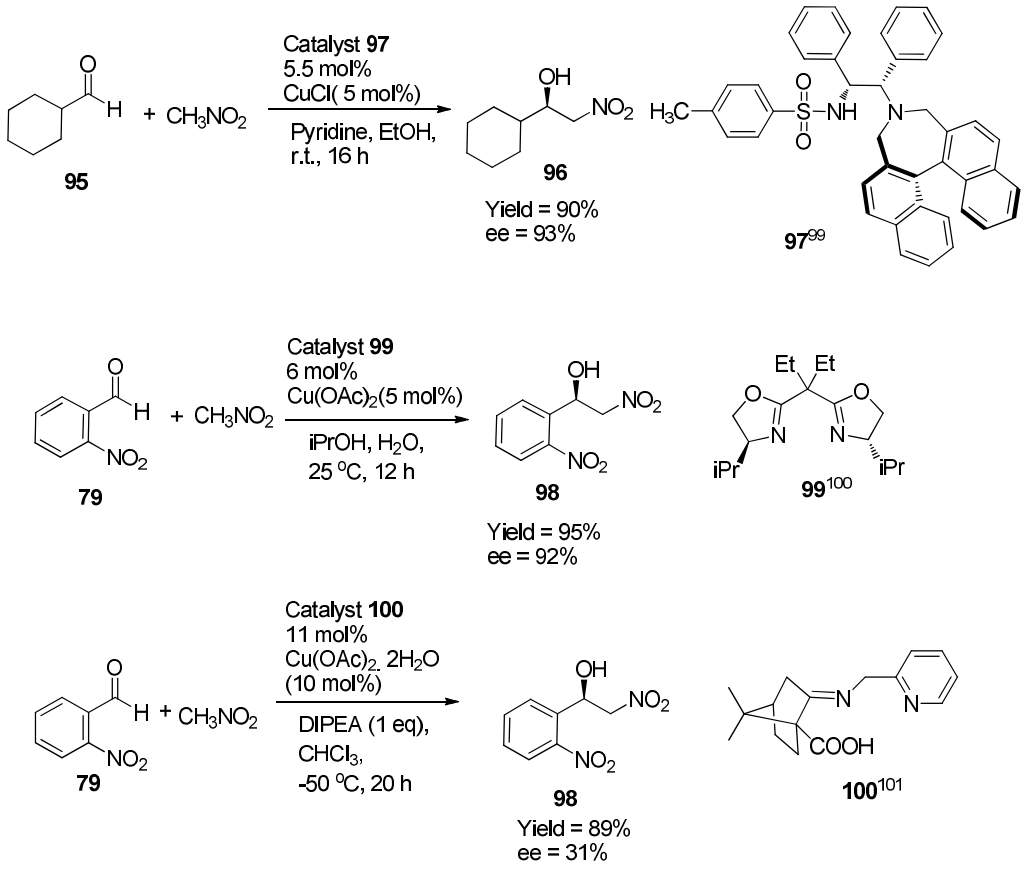


Figure 13: Chiral ligands developed for Henry reactions.

1.3.2.4 Diels-Alder reaction

Asymmetric Diels-Alder reactions are very useful for synthesising bicyclic derivatives and can be used to synthesise chiral building blocks. This reaction is a fundamental C-C bond forming reaction and during this process, cyclic rings are constructed with a number of stereocenters.[51,102] Thus, it is another of the areas in which research groups are working to develop efficient asymmetric organocatalysts (Figure 14).[51,102-103]

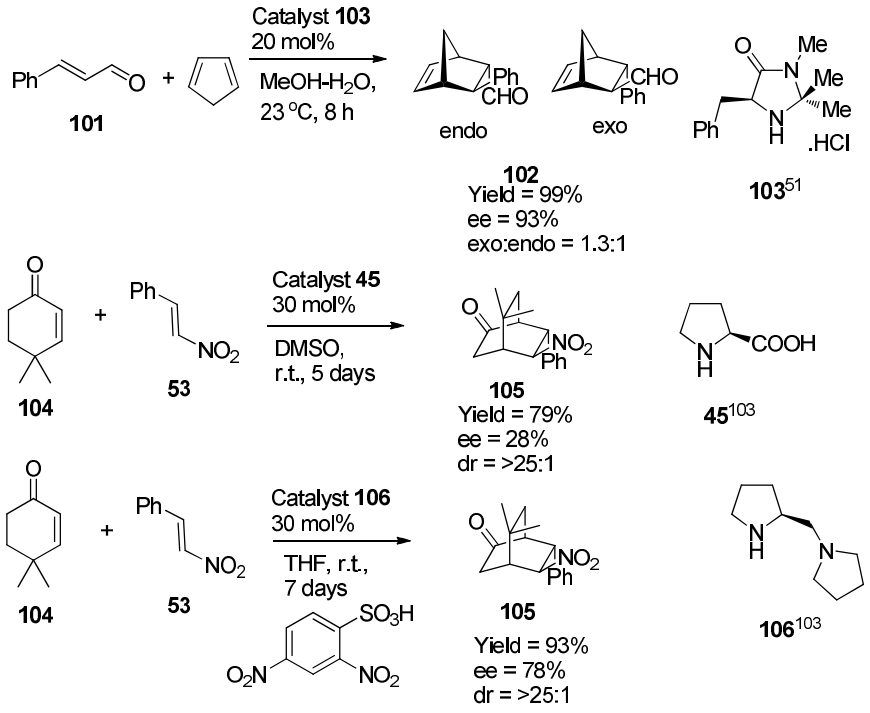


Figure 14: Asymmetric organocatalysts for asymmetric Diels-Alder reactions.

1.3.2.5 α-Functionalization of carbonyl compounds

In the synthesis of small molecules, introduction of -N, -O, -S and -halogen at α-position of aldehydes or ketones are useful transformations. The resulting products can be transformed into chiral building blocks, biologically important molecules and even new chiral ligands. The asymmetric Strecker[104-107] and Mannich[108-112] reactions

are already known and used for C-C bond formation by addition of imines. Direct C-N bond formation reaction is quite interesting as it directly gives a chiral molecule containing a chiral centre bearing a nitrogen substituent. The direct asymmetric C-N bond formation using organocatalysts has opened a new path in asymmetric organocatalysis, as the resulting chiral products include α-amino acids, α-amino aldehydes and α-amino alcohols which are very important in organic synthesis.

In C-N bond formation, azodicarboxylates may be used as a source of nitrogen groups. The resulting addition product can be converted into an alcohol, amine or oxazolidinone ring.[113-117] The following asymmetric organocatalysts have been found to be efficient and selective for the addition of aldehyde or ketone to azodicarboxylate (Figure 15).[116-117]

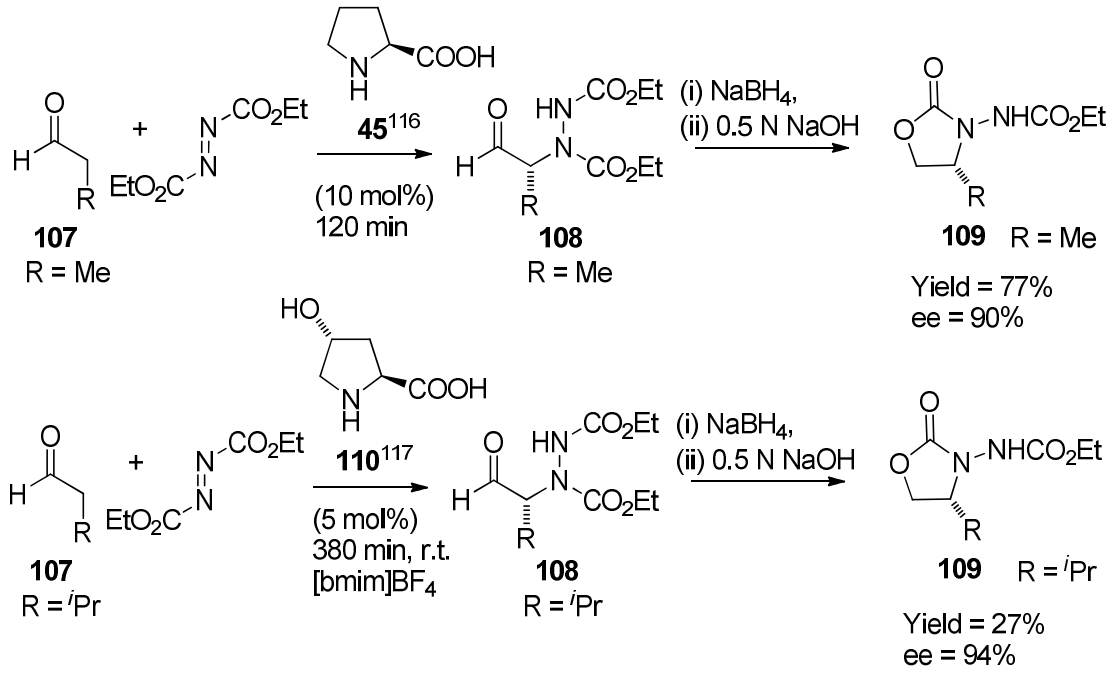


Figure 15: Asymmetric organocatalysts for asymmetric C-N bond formation reaction.

Proline and its derivatives, bifunctional catalysts and MacMillan's type of catalysts have been found to be good for the addition reaction,[118] α-functionalization of aldehydes or ketones,[119-125] epoxidation of α,β- unsaturated carbonyl compounds,[126] γ-amination of α,β-unsaturated carbonyl compounds,[127] addition of thioacetic acid to nitroalkenes,[128] and addition of nitroalkanes to enones.[129].

These applications of asymmetric organocatalysts, have inspired different research groups to find more interesting and challenging application of organocatalysts in asymmetric synthesis.[130-136]

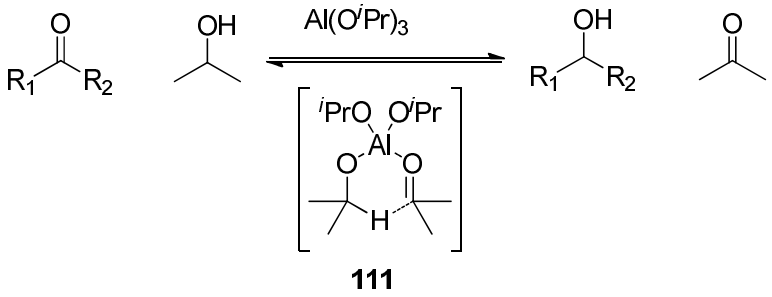
1.4 Asymmetric transfer hydrogenation

The pressure hydrogenation is a well developed area which requires the use of gaseous hydrogen.[21-23] In contrast, transfer hydrogenation requires use of small molecules as source of hydrogen instead. Commercially used hydrogen donors include alcohols as used in Meerwein-Ponndorf-Verley reduction. Transfer hydrogenation often makes the reaction much easier to handle, safer and quite easy to analyse. Due to this, asymmetric transfer hydrogenation has become an economical and environmental friendly method to synthesise different chiral molecules with applications in pharmaceuticals, functional materials and in natural product synthesis.

1.4.1 Background

The first known example of transfer hydrogenation of carbonyl compounds was the Meerwein-Ponndorf-Verley reduction discovered in 1925.[137-139] The MPV reduction involves the reduction of ketones and aldehydes to corresponding alcohols by

aluminium isopropoxide in alcohol (Scheme 9).[137] In earlier reaction conditions, it was required to use stoichiometric amount of aluminium isopropoxide. Use of a catalytic amount of aluminium reagent was reported by Nguyen group.[140] The MPV reduction is a homogenous reduction while heterogeneous reductions have also been developed.[141] The mechanistic cycle of MPV involves coordination of the carbonyl group with the Lewis acidic aluminium isopropoxide, followed by hydride transfer from one of the isopropoxide molecule (**111**) (Scheme 9).



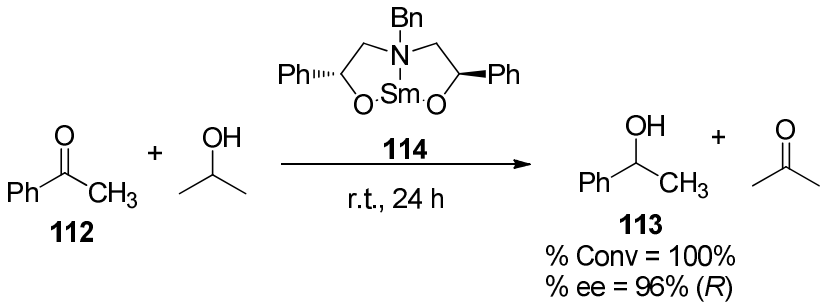
111

Scheme 9: MPV reduction.

Stereoselective MPV reduction can be achieved by (1) use of a chiral alcohol as a hydride donor, (2) intramolecular MPV reduction, or (3) use of chiral ligands. The MPV reduction has been developed with use of Lanthanide alkoxide[142] and lanthanide.[143] The rhodium complexes with chiral ligand derived from phennanthroline were studied for asymmetric transfer hydrogenation of acetophenone with high conversion and good selectivities.[144] Bäckvall *et al*. have reported the transfer hydrogenation of ketones using $RuCl_2(PPh_3)_3$ and NaOH in IPA.[145]

Evans *et al*. have reported the use of chiral Sm compound for enantioselective MPV type reduction of different aryl methyl ketones with 68-96% ee.[146] The reduction of acetophenone was carried out using the chiral Sm catalyst **114** in IPA at room

temperature for 24 h to give a product in 100% conversion and 96% ee (Scheme 10).[146]



Scheme 10: Asymmetric transfer hydrogenation of acetophenone using chiral Sm compound **114**.

1.4.2 Hydrogen sources

In earlier work, isopropanol was used as the hydrogen donor, together with a base such as sodium or potassium hydroxide, alkoxides or carbonates. During this process, isopropanol generates acetone, which can undergo a reversible process. Most of the asymmetric transfer hydrogenation reactions were carried out with IPA/KOH; under these conditions most of the metal complexes were stable enough to give good selectivity. At the lower temperature, this method gives the kinetically stable product and as the reaction progresses the rate of the reverse reaction becomes higher and acetone is converted back to IPA.[147] This results in a drop of selectivity. Even the rate of the reverse reaction is dependent on the oxidation potentials[148] of the substrate, and 100% conversion using IPA is difficult to achieve. To overcome this drawback the removal of acetone during the reaction or the use of high dilution methods is required.

Formic acid and its salts are well known as a source of hydride back to 1885 and 1905 for reaction such as the Leuckart-Wallach reaction[149] (reductive amination of

aldehyde using ammonium formate) and Eschweiler–Clarke reaction[150] (methylation of primary or secondary amine). During both processes, formic acid gives CO_2 as a byproduct, which can be easily removed from the reaction. Formic acid has been used as the source of hydrogen with a base or as an azeotropic mixture with base in asymmetric transfer hydrogenations. An azeotropic mixture containing formic acid: triethylamine (5:2) has been found to be a more efficient,[151] easy to handle, single phase reaction with a range of solvents. This mixture works well with temperature from 20-60 ^{o}C and a high concentration of substrate compared to IPA/KOH. In asymmetric transfer hydrogenation, different small molecules have been used as the source of hydrogen including isopropanol, formic acid, formic acid:triethylamine azeotrope and sodium formate depending on the solubility, stability and activity of different chiral metal complexes.

1.4.3 Ligand developments for asymmetric transfer hydrogenation

A review on some of the ligands developed for asymmetric transfer hydrogenation is presented in this section. Asymmetric transfer hydrogenation for acetophenone (**112**) is used as a model reaction, unless otherwise stated, for comparison of ligands and metal complexes or with isolated complexes under reported conditions.

1.4.3.1 Tetrahydro bis(oxazole) ligands

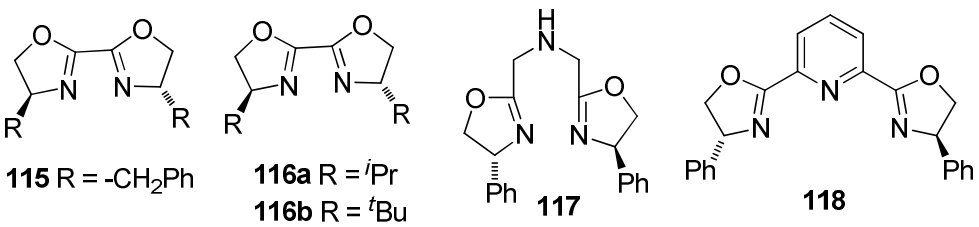


Figure 16: Oxazole derivatives.

In 1991, Pfaltz *et al*. reported the synthesis and application of derivatives of tetrahydro bis(oxazole) as ligands for enantioselective reduction of aryl alkyl ketones (Figure 16).[152] Compounds **115-116** were used for reduction of acetophenone with the metal complex $[Ir(COD)Cl_2]_2$ using IPA/KOH at 80 ^oC. Compound **115** gave a good conversion up to 89% and low enantioselectivity with 47% ee for reduction of acetophenone in combination with $[Ir(COD)Cl_2]_2$ (Table 1). More interesting results were obtained using compound **116a-b**. Compound **116a** gave 89% conversion and 58% ee within 3 h. While compound **116b** with the hindered *tert*-butyl group, failed to give any significant conversion under similar conditions (Table 1).[152]

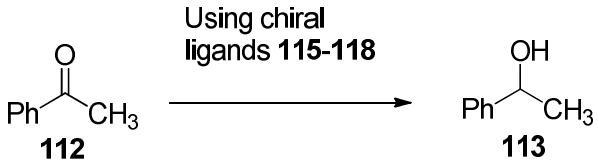


Table 1: Asymmetric transfer hydrogenation of acetophenone **112** using bis(oxazole) derivatives as chiral ligands **115-118**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Conv	% ee
115	$[Ir(COD)Cl_2]_2$	IPA/KOH	100	80 ^oC	3 h	89	47(*R*)
116a	$[Ir(COD)Cl_2]_2$	IPA/KOH	100	80 ^oC	3 h	89	58(*R*)
116b	$[Ir(COD)Cl_2]_2$	IPA/KOH	100	80 ^oC	3 h	<5	-
117	$Ru(PPh_3)_2Cl_2$	IPA/NaO^{i}Pr	100	82 ^oC	10 min	91	97(*S*)
118	$Sn(OTf)_2$	MeOH/ PMHS	10	r.t.	12-14 h	95	58(*R*)

Modified C_2-symmetric ligands with different bridges between the two oxazole molecules have been reported as tridentate ligands for enantioselective transfer hydrogenation (Figure 16).[153-154] Compound **117** with an amine bridge was used for

acetophenone reduction with $Ru(PPh_3)_2Cl_2$ using IPA/NaO^{i}Pr at 82 ^oC. Compound **117** gave a very high conversion of 95 % within 10 min with high enantioselectivity of 97% ee (Table 1).[153] The pyridine bridged compound **118** was employed for enantioselective reduction of ketones using $Sn(OTf)_2$ and polymethylhydrosiloxane (PMHS) as the reducing agent. Compound **118** gave a good conversion (95%) over a period of 12-14 h, but enantioselectivity was quite low (58% ee) (Table 1).[154]

1.4.3.2 Diamine ligands

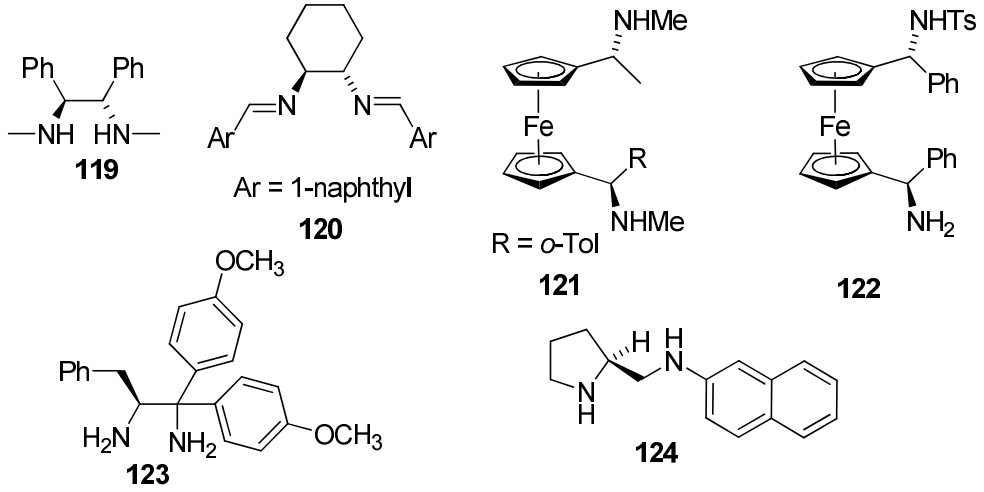


Figure 17: Diamine derivatives.

Lemaire *et al*. have reported the use of C_2 symmetric diamine as chiral ligands with $[Rh(C_6H_{10})Cl]_2$ for asymmetric transfer hydrogenation of carbonyl compound in IPA/KOH.[155] The best results were obtained with compound **119**. For acetophenone reduction, it gave 100% conversion over a period of 7 days with 67% ee with $[Rh(C_6H_{10})Cl]_2$ (Figure 17, Table 2).[155]

Alper and Krasik reported series of compounds derived from 1,2-diamino cyclohexane for asymmetric transfer hydrogenation using IPA.[156] All derivatives were applied to acetophenone reduction with $[Ru(C_6H_6)Cl_2]_2$ using IPA/KOH under

reflux. Only compound **120** was found to give a useful result with 89% yield and 28% ee (Figure 17, Table 2).[156]

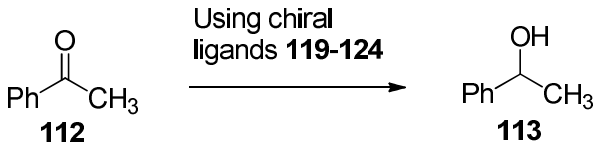


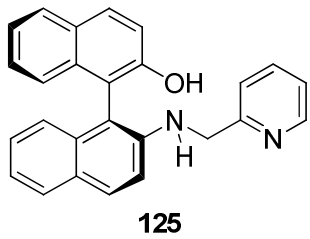
Table 2: Asymmetric transfer hydrogenation of acetophenone **112** using diamine derivatives as chiral ligands **119**-**124**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
119	$[Rh(C_6H_{10})Cl]_2$	IPA/KOH	100	r.t.	7 days	100	67(*R*)
120	$[Rh(C_6H_{10})Cl]_2$	IPA/KOH	100	Reflux	2-8 h	89	28(*S*)
121	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	100	-30 ^oC	120 h	95	80(*R*)
122	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	100	22 ^oC	24 h	97	56(*R*)
122	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	100	33 ^oC	120 h	42	83(*R*)
123	[Ir(COD)Cl_2]$_2$	IPA/KOH	250	r.t.	12 h	74	78(*R*)
124	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaO^{i}Pr	100	25 ^oC	0.5 h	89	91(*S*)

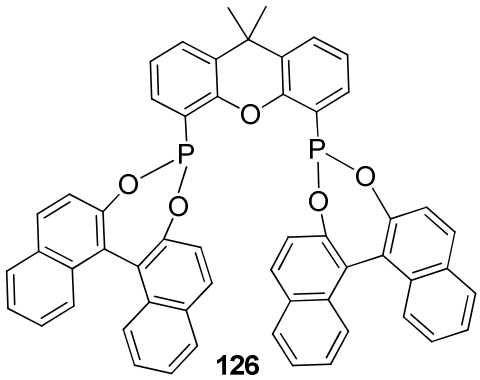
In 1996, Knochel *et al*. reported a series of C_2 symmetrical ferrocene derivatives as chiral ligands for enantioselective transfer hydrogenation with Ru(*p*-cymene)Cl_2]$_2$.[157] Compound **121** was found to be good for reduction of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ using IPA/KOH at -33 ^oC. It gave 95% conversion over a period of 120 h with 85% ee (Figure 17, Table 2).[157] Compound **122** was used under similar conditions with [Ru(*p*-cymene)Cl_2]$_2$ at 22 ^oC to give 97% conversion with a drop in ee (56% ee). When compound **122** was employed for transfer hydrogenation with [Ru(*p*-cymene)Cl_2]$_2$ using FA:TEA at 33 ^oC, the enantioselectivity was 83% ee with a drop in conversion to 42% (Table 2).[157]

Diamine derivatives like compound **123** were used with $[Ir(COD)Cl_2]_2$ for asymmetric transfer hydrogenation of various ketones.[158] Compound **123** was found to be good for acetophenone reduction with $[Ir(COD)Cl_2]_2$ at room temperature over a period of 12 h with 74% conversion and 78% ee (Figure 17, Table 2). Compound **123** was found to be good with $[Ir(COD)Cl_2]_2$ for enantioselective transfer hydrogenation of different ketones with 21-93% ee.[158] Various diamines derived from proline have been reported as chiral ligands for asymmetric transfer hydrogenation.[159] Compound **124** gave a good conversion 89% in 0.5 h at room temperature and high enantioselectivity of 91% ee for acetophenone reduction with $[Ru(p\text{-cymene})Cl_2]_2$ using IPA/NaO^{i}Pr (Figure 17, Table 2).[159]

1.4.3.3 Binol derivatives



125

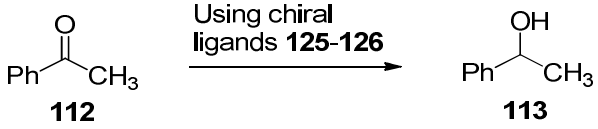


126

Figure 18: Binol derivatives.

Chiral complexes of Ru with derivatives of BINOL have been synthesised and used for asymmetric transfer hydrogenation to give conversion up to 98% and enantioselectivity up to 97% ee in ketone reduction.[160] One representative example, compound **125** with $Ru(PPh_3)_2Cl_2$ gave a product in 94% yield and 96.7% ee in 15 h at 28 ^oC for transfer hydrogenation of acetophenone using IPA/ KO^{t}Bu (Figure 18, Table 3).[160]

Reetz and Li reported the use of different BINOL derived diphosphinites as chiral ligands for asymmetric transfer hydrogenation.[161] Compound **126** was found to be good compared to other derivatives for the reduction of acetophenone (Figure 18, Table 3). Compound **126** gave high conversion 93% and high enantioselectivity 98% ee at 40 ^{o}C in 40 h using [Ru(*p*-cymene)Cl_2]$_2$ as the metal source and NaOH as the base in IPA.[161] Compound **126** also worked well for a range of aryl alkyl ketones with conversion in the range of 56-100% and enantioselectivity in the range of 76-99% ee in combination with [Ru(*p*-cymene)Cl_2]$_2$.[161]



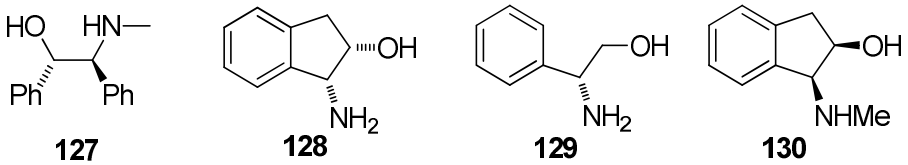
112 **113**

Table 3: Asymmetric transfer hydrogenation of acetophenone **112** using diamine derivatives as chiral ligands **125-126**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
125	$Ru(PPh_3)_2Cl_2$	IPA/ KO^{t}Bu	100	28 ^{o}C	15 h	94.3	96.7(*S*)
126	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	200	40 ^{o}C	40 h	93	98(*R*)

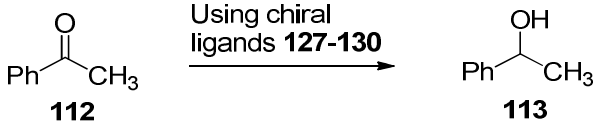
1.4.3.4 Amino alcohol derivatives

Noyori *et al*. reported amino alcohol derivatives with different Ru(arene) metal complexes as efficient catalysts for asymmetric transfer hydrogenation using IPA/KOH.[162] The best result for acetophenone reduction was obtained with compound **127** and [Ru(HMB)Cl_2]$_2$ at 28 ^{o}C which gave, in 1h, a product of 94% yield and 92% ee (Figure 19, Table 4).[162]



127 **128** **129** **130**

Figure 19: Amino alcohol derivatives.



112 **113**

Table 4: Asymmetric transfer hydrogenation of acetophenone **112** using amino alcohols **127-130** as chiral ligands.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
127	$[Ru(HMB)Cl_2]_2$	IPA/KOH	200	28 ^oC	1 h	94	92(*S*)
128	$[Ru(p\text{-cymene})Cl_2]_2$	IPA/KOH	200	r.t.	1.5 h	70	91(*S*)
129	$[Ru(p\text{-cymene})Cl_2]_2$	IPA/KOH	200	r.t.	2 h	95	23(*S*)
130	$[Ru(p\text{-cymene})Cl_2]_2$	IPA/KOH	200	r.t.	2 h	95	23(*S*)

Wills has reported the use of chiral amino alcohols derived from aminoindanols as chiral ligands for asymmetric transfer hydrogenation.[163] Compound **128** was found to be good with $[Ru(p\text{-cymene})Cl_2]_2$ in IPA/KOH for reduction of acetophenone with 70% conversion and 91% ee within 1.5 h at room temperature (Figure 19, Table 4). While the less rigid compound **129** gave a good conversion using $[Ru(p\text{-cymene})Cl_2]_2$under similar conditions with a high drop in selectivity.[163] The -*N*Me analogue compound **130** also showed a similar drop in enantioselectivity under the reaction conditions in combination with $[Ru(p\text{-cymene})Cl_2]_2$ (Figure 19, Table 4). Results obtained for acetophenone reduction using compound **128** and **129**, clearly show the importance of rigidity and -*N*H in this series of compounds.[163]

Andersson *et al*. reported a series of amino alcohols as chiral ligands with Ru for asymmetric transfer hydrogenation.[164] Compound **131** (prolinol) was found to be poor as a chiral ligand with $[Ru(HMB)Cl_2]_2$ using IPA/KOH with very low conversion (16%) and enantioselectivity (8% ee) (Figure 20, Table 5). The bicyclic alcohol derivative (1*S*,3*R*,4*R*) compound **132** gave a very high conversion of 92% and enantioselectivity of 95% ee with $[Ru(HMB)Cl_2]_2$ at room temperature within 5 h for acetophenone.[164] While the substituted analogue (1*S*,3*R*,4*R*) compound **133** gave high conversion but a total loss in enantioselectivity under the similar reaction conditions in combination with $[Ru(HMB)Cl_2]_2$ (Figure 20, Table 5).[164]

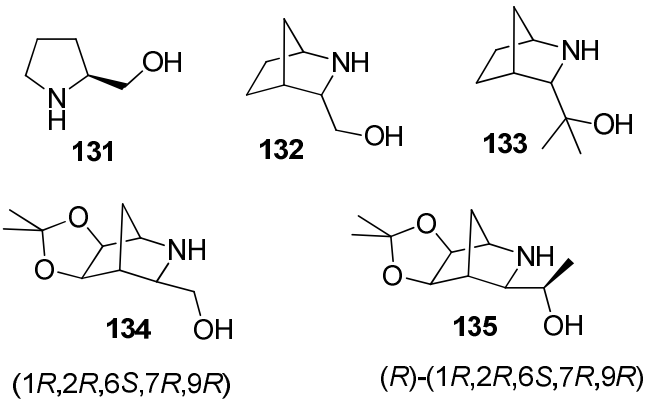


Figure 20: Amino alcohol derivatives.

In 2001, the same group reported different derivatives of bicyclic amino alcohols for the transfer hydrogenation of ketones.[165] Compound **134** gave 92% conversion and 96% ee in 1 h with $[Ru(p\text{-cymene})Cl_2]_2$ using IPA/KOH (Figure 20, Table 5). Compound **135** was found to be highly active for the transfer hydrogenation of acetophenone with $[Ru(p\text{-cymene})Cl_2]_2$ using IPA/KOH (Figure 20, Table 5).[165] Compound **135** gave 97% conversion within 0.25 h and in a high enantioselectivity of 96% ee for asymmetric transfer hydrogenation of acetophenone with $[Ru(p\text{-cymene})Cl_2]_2$. Compound **135** was studied at different S/C ratios and was found to

be highly effective up to a S/C ratio of 5000 with [Ru(*p*-cymene)Cl_2]$_2$ which gave similar high conversions and enantioselectivity in 90 min reaction time (Table 5).[165]

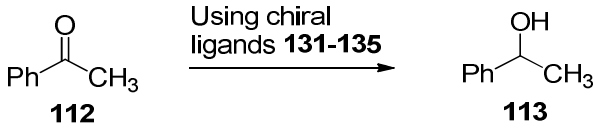


Table 5: Asymmetric transfer hydrogenation of acetophenone **112** using amino alcohols **131-135** as ligands.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
131	[Ru(HMB)Cl_2]$_2$	IPA/KOH	200	r.t.	6.5 h	16	8(*S*)
132	[Ru(HMB)Cl_2]$_2$	IPA/KOH	200	r.t.	5 h	92	95(*S*)
133	[Ru(HMB)Cl_2]$_2$	IPA/KOH	200	r.t.	16 h	85	Rac
134	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	100	r.t.	1 h	92	96(*S*)
135	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	100	r.t.	0.25 h	97	96(*S*)
135	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	200	r.t.	6 min	96	96(*S*)
135	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	5000	r.t.	90 min	97	96(*S*)

1.4.3.5 Ferrocene Ru complexes

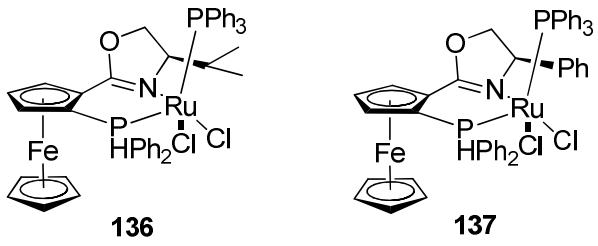


Figure 21: Ferrocene Ru complexes.

The Hidai group has reported highly active Ru-ferrocene complexes for the asymmetric transfer hydrogenation of different ketones.[166] Compounds **136** and **137** were found to be very selective for the transfer hydrogenation of acetophenone

giving up to 95% conversion and >99% ee in 2 h at room temperature using IPA/NaO^{i}Pr (Figure 21, Table 6).[166]

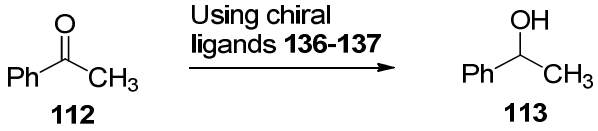


Table 6: Asymmetric transfer hydrogenation of acetophenone **112** using complexes **136-137**.

Compd	Hydrogen source	S/C	Temp	Time	% Yield	% ee
136	IPA/ NaO^{i}Pr	200	r.t.	2 h	94	>99.6 (*R*)
137	IPA/ NaO^{i}Pr	200	r.t.	2 h	95	>99.7(*R*)

1.4.3.6 Tridentate ligands

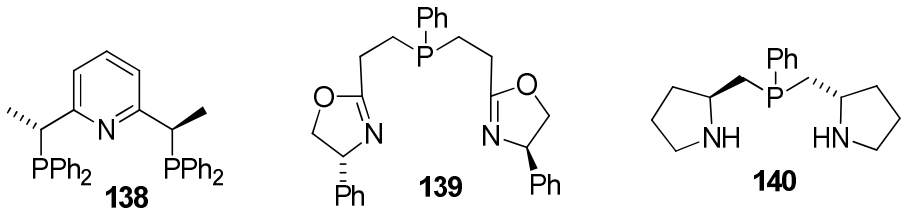


Figure 22: Tridentate ligands.

In 1996, Zhang reported C_2 symmetric tridentate ligands for the asymmetric transfer hydrogenation of ketones with $[RuCl_2(C_6H_6)]_2$.[167] Compound **138** gave a good conversion of 91%, but very low enantioselectivity of 35% ee in 24 h at room temperature with $[RuCl_2(C_6H_6)]_2$ using IPA/NaOMe (Figure 22, Table 7).[167]

The same author reported NPN type tridentate chiral ligands for the asymmetric transfer hydrogenation in 1997.[168-169] Compound **139** has shown comparable result for the reduction of acetophenone using $[RuCl_2(C_6H_6)]_2$ with 72% conversion and a good ee of 79% within 0.2 h at 80 ^{o}C in IPA/KOH (Figure 22, Table 7).[168] The

tridentate compound **140**, gave a good conversion (96%) but very low enantioselectivity (19.8% ee) for acetophenone reduction using $[RuCl_2(C_6H_6)]_2$and IPA/NaO^{i}Pr (Table 7).[169]

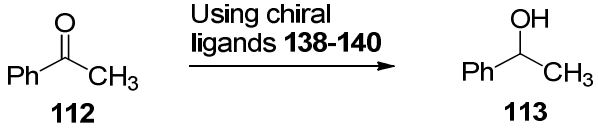


Table 7: Asymmetric transfer hydrogenation of acetophenone **112** using chiral ligands **138**-**140**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
138	$[RuCl_2(C_6H_6)]_2$	IPA/NaOMe	100	r.t.	24 h	91	35(*R*)
139	$[RuCl_2(C_6H_6)]_2$	IPA/KOH	100	80 ^oC	0.2 h	72	79(*R*)
140	$[RuCl_2(C_6H_6)]_2$	IPA/ NaO^{i}Pr	100	23 ^oC	24 h	96	19.8(*R*)

1.4.3.7 Tetradentate ligands

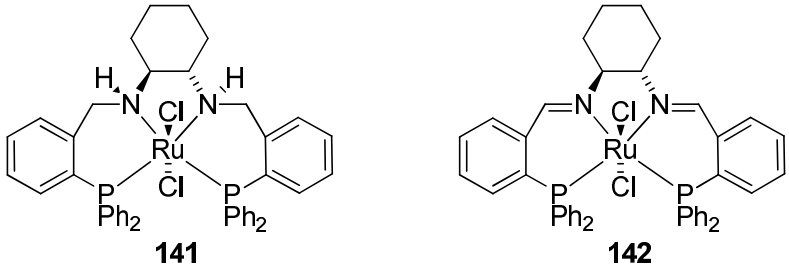


Figure 23: Tetradentate ligands.

Noyori *et al*. have reported the chiral-Ru complexes with C_2 symmetric diphosphino/diamino tetradentate ligands for asymmetric transfer hydrogenation of aromatic ketones (Figure 23).[170] Compound **141** was found to be good with a 91% conversion and highly selective, giving a product of 97% ee for acetophenone

reduction in 25 h at 23 ^{o}C in IPA/KOH (Table 8). On the other hand, compound **142** gave very low conversion and selectivity for transfer hydrogenation of acetophenone under similar conditions (Table 8).[170]

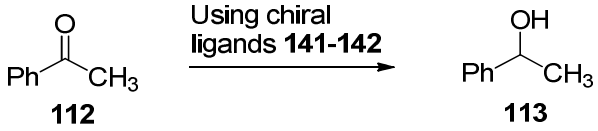


Table 8: Asymmetric transfer hydrogenation of acetophenone **87** using chiral ligands **141**-**142**.

Compd	Hydrogen source	S/C	Temp	Time	% Yield	% ee
141 (*S*,*S*)	IPA/KOH	200	23 ^{o}C	25 h	91	97(*S*)
142 (*S*,*S*)	IPA/KOH	200	23 ^{o}C	48 h	3	18(*S*)

1.4.3.8 Peptide ligands

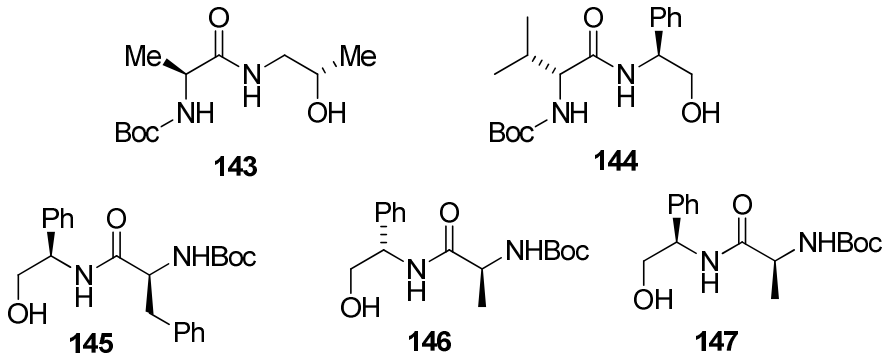
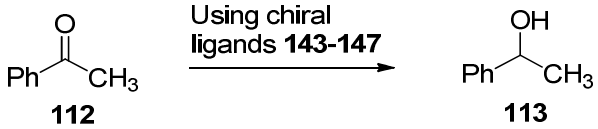


Figure 24: Peptide ligands.

Adolfsson *et al*. have reported a series of peptide ligands for Ru catalysed asymmetric transfer hydrogenation of ketones.[171] Compound **143** and **144** gave a good conversions of up to 90-92% and high enantioselectivities of 93-96% ee for the transfer hydrogenation of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ in IPA/NaOH at room temperature in 2h (Figure 24, Table 9).[171]

Wills *et al*. have also reported a series of peptide derivatives as chiral ligands for asymmetric transfer hydrogenation of ketones.[172] Differently substituted compounds were studied for the reduction of acetophenone to understand the mechanism and requirement for a free alcohol group. Compounds **145**-**147** gave comparable conversions of 31-80% with enantioselectivities of 88-91% ee for the reduction of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ in IPA/NaOH at room temperature in 2 h (Figure 24, Table 9).[172]



112 **113**

Table 9: Asymmetric transfer hydrogenation of acetophenone **112** using chiral ligands **143**-**147**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
143	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	100	r.t.	2 h	90	96(*S*)
144	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	100	r.t.	2 h	92	93(*R*)
145	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	100	r.t.	2 h	31	91(*S*)
146	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	100	r.t.	2 h	76	88(*S*)
147	[Ru(*p*-cymene)Cl_2]$_2$	IPA/NaOH	100	r.t.	2 h	80	90(*S*)

1.4.3.9 Monotosylated 1,2-diamine derivatives

A major breakthrough was obtained in 1995 by the Noyori group in the use of monotosylated 1,2-diamines as chiral ligands for Ru catalysed transfer hydrogenation.[173] Compound **64** (TsDPEN) gave very high conversion of 95% and high enantioselectivity of 97% ee with [Ru(mesitylene)Cl_2]$_2$ in IPA/KOH for asymmetric transfer hydrogenation of acetophenone at room temperature in 15 h

(Figure 25, Table 10).[173] Compound **64** exhibited similar activity for a range of ketones with 45-98% conversion and 72-98% ee.

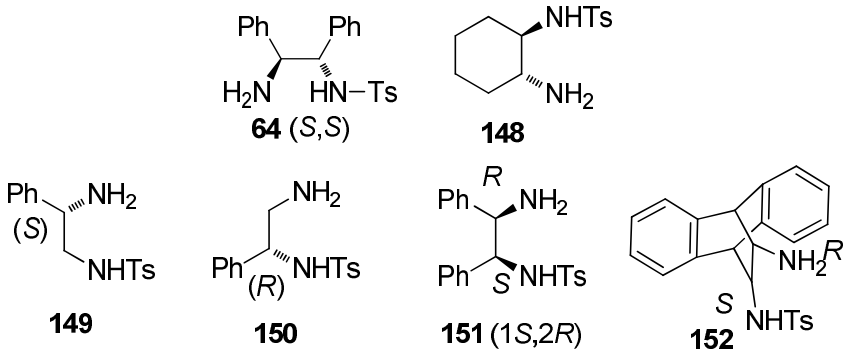


Figure 25: Monotosylated 1,2-diamine derivatives.

In 1996, Knochel reported monotosylated 1,2-cyclohexanediamine as a chiral ligand for enantioselective transfer hydrogenation.[157a] Compound **148** gave a very high conversion of 97% with [Ru(*p*-cymene)Cl_2]$_2$ at room temperature in 24 h in IPA/KOH, but the enantioselectivity was just comparable at 89% ee for acetophenone reduction (Figure 25, Table 10). When compound **148** was used for a similar reaction with [Ru(*p*-cymene)Cl_2]$_2$ in FA:TEA as the hydrogen source, a product was formed in 99% conversion and 94% ee (Table 10).[157a]

The Wills group have reported a series of monotosylated diamine derivatives in order to establish the importance of 1,2-*anti*-disubstitution in monotosylated diamines.[174] Compounds **64**, **149**-**151** were employed for the reduction of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ using FA:TEA as the hydrogen source (Figure 25, Table 10). As already reported, compound **64** gave complete conversion with 98% ee for acetophenone reduction in combination with [Ru(*p*-cymene)Cl_2]$_2$ in 22h at 28 ^{o}C. Compound **149** was found to be slow compared to 64 for reduction of acetopheneone with [Ru(*p*-cymene)Cl_2]$_2$, with 95% conversion in 48 h and moderate enantioselectivity (69% ee).[174] In contrast, compound **150** in combination with

[Ru(*p*-cymene)Cl_2]$_2$, showed almost total loss in catalytic activity with 48% conversion and 33% ee over a long reaction period of 13 days (Table 10). The *syn* analogue of compound **64**, compound **151**, was also found to be slow and less efficient compared to **64**, with 32% conversion and 70% ee at 28 ^oC in 220 h using [Ru(*p*-cymene)Cl_2]$_2$ (Table 10). Results obtained for compounds **149-151**, clearly show the importance of *anti*-disubstitution in diamine ligands.[174]

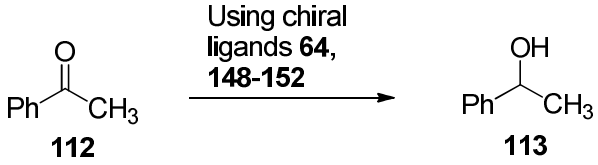


Table 10: Asymmetric transfer hydrogenation of acetophenone **112** using chiral ligands **64**, **148**-**152**.

Ligands	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
64	[Ru(mesitylene)Cl_2]$_2$	IPA/KOH	200	r.t.	15 h	95	97(*S*)
148	[Ru(*p*-cymene)Cl_2]$_2$	IPA/KOH	100	22 ^oC	24 h	97	89(*R*)
148	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	100	33 ^oC	24 h	99	94(*R*)
64	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	200	28 ^oC	22 h	100	98(*R*)
149	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	200	28 ^oC	48 h	95	69(*S*)
150	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	200	28 ^oC	13 days	46	33(*R*)
151	[Ru(*p*-cymene)Cl_2]$_2$	FA:TEA	200	28 ^oC	220 h	32	70(*S*)
152	[Ru(C_6H_6)Cl_2]$_2$	FA:TEA	200	25 ^oC	15 h	98	93(*S*)

Chiral-Ru(arene) complex of a "roofed" *cis*-diamine has been reported by Ishizuka group for asymmetric transfer hydrogenation of ketones.[175] The preformed catalyst of compound **152** with [Ru(C_6H_6)Cl_2]$_2$, gave high conversion of 98% and enantioselectivity of 93% ee at 25 ^oC in 15 h for the asymmetric transfer

hydrogenation of acetophenone (Figure 25, Table 10). The preformed complex of compound **152** with $[Ru(C_6H_6)Cl_2]_2$ was found to be good for a range of ketones in asymmetric transfer hydrogenation.[175]

1.4.4 Mechanistic investigations of asymmetric transfer hydrogenation of ketones and imines

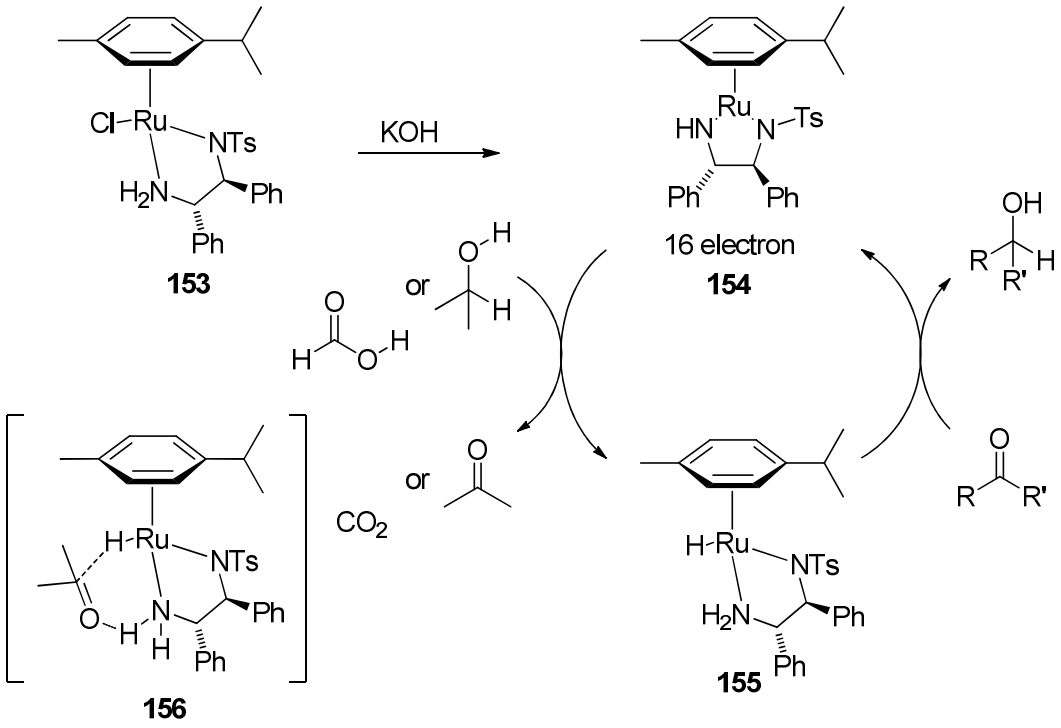


Figure 26: Mechanistic cycles in asymmetric transfer hydrogenation of ketones.

The combination of (1*S*,2*S*) TsDPEN (**64**) and $[Ru(p\text{-cymene})Cl_2]_2$ was reported to give the complex **153** as orange crystals.[176] This chloride complex **153** is converted to the 'true' active catalyst - "an amido complex **154**" - with base in IPA and is formed with a characteristic purple colour. Amido complex **154** is a 16-electron neutral complex having square–planar geometry and the metal bound to two anionic nitrogen atoms. This amido complex **154** reacts with IPA to give a single diastereomer of amine hydrido Ru complex **155** as a yellow powder. This

amine hydrido Ru complex **155** is an 18-electron complex, and acts as the hydride source in asymmetric reductions (Figure 26).[176]

For ketone reduction, Noyori has proposed that this transfer takes place *via* the cyclic six-membered transition state depicted in a reversible manner **156.**[177] For the Ir complex **158**, the 16 electron and hydride complex were synthesised by a method similar to the chiral Ru complex **153**. While for the Rh complex **157** only the 16 electron species was detected.[178] Related studies were carried out by Ikariya *et al*. for Cp*Rh and Cp*Ir complexes having chiral ligands TsCYDN and TsDPEN using KO^{t}Bu in IPA for transfer hydrogenation of aromatic ketones. The isolation and catalytic study of Cp*IrH(*R*,*R*)TsCYDN **160** proved it to have a similar catalytic cycle as observed for RuCl(*p*-cymene)TsDPEN complex **153** (Figure 27).[179]

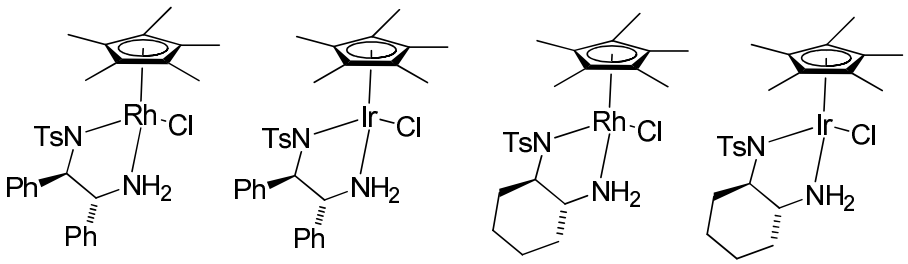


Figure 27: Cp*Rh and Cp*Ir complexes.

The transfer of hydrogen between the alcohol and ketone by chiral-Ru(arene) complexes has been well studied by different methods. In 2003, Casey reported the kinetic isotope effect in the dehydrogenation of deuterated isopropanol by amido Ru complex.[180] It was found that the hydride and proton transfer occur simultaneously, which again confirms the metal ligand bifunctional catalysis mechanism proposed by Noyori.[180] All these studies have indicated that transfer hydrogenation using IPA takes place through a six membered pericyclic transition state.

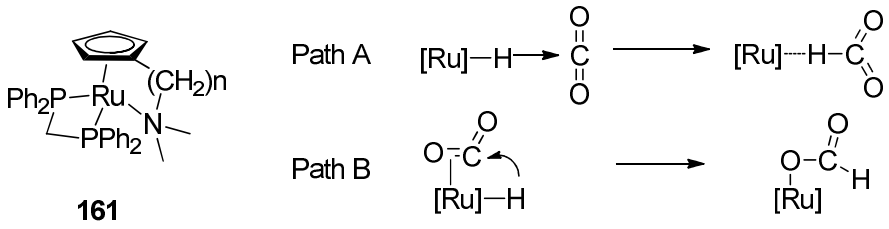


Figure 28: Possible path for transfer of hydride from metal to CO_2.

Most of the recent asymmetric transfer hydrogenation reactions were developed using formic acid: triethylamine (5:2). Matsubara has reported the DFT study on the transfer of hydride from complex **161** to CO_2 (Figure 28). He has described two possible paths for this transformation and shown that path A with a low energy barrier of 2.6 kcal/mol, is more favourable (Figure 28).[181]

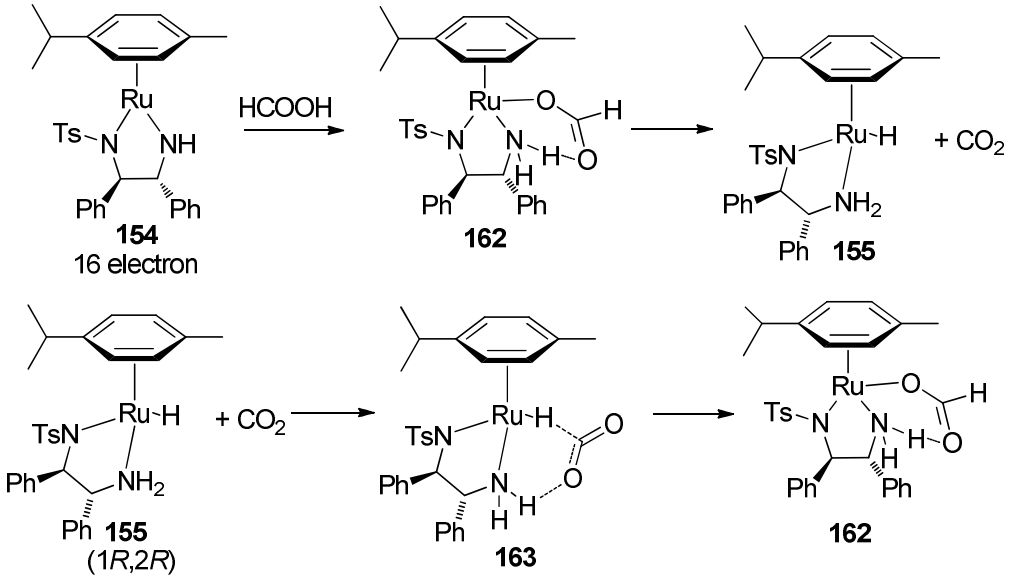


Figure 29: Reaction of amide complex **154** with formic acid and hydride complex **155** with CO_2.

In 2004, Ikariya reported detailed mechanistic and experimental studies on the reaction of amide complex **154** with formic acid.[182] This was followed by formation of an ion pair intermediate, in contrast to the concerted process with IPA. The

formate complex **162** gives amino Ru complex **155** by decarboxylation. Moreover, hydrido Ru complex **155** reacts with CO_2 to form formate complex **162** *via* intermediate **163** (Figure 29). Thus, hydrido Ru complex **155** catalyses the hydrogenation of CO_2 to give formic acid. Due to this reversible process in the reaction, it is important to remove the CO_2 generated in the asymmetric reduction with formic acid (Figure 29).[182] Recently, a similar study was reported using DFT calculation by Whitwood, for the formation of a formate complex in Rh(III) catalysed transfer hydrogenation.[183]

Stroatman *et al*. have also reported the effect of CO_2 on the asymmetric reductive amination catalysed by compound **153**.[184] The rate of reaction was affected by CO_2 formed during the reaction with a drop in yield and selectivity. The equilibrium between Ru-formate complex **164** and Ru-hydrido complex **155** was affected by CO_2 (Figure 30). This can be altered by purging CO_2 from reaction mixture or trapping CO_2 with secondary amines.[184]

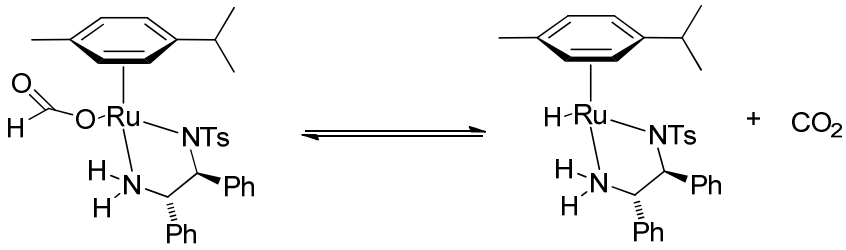
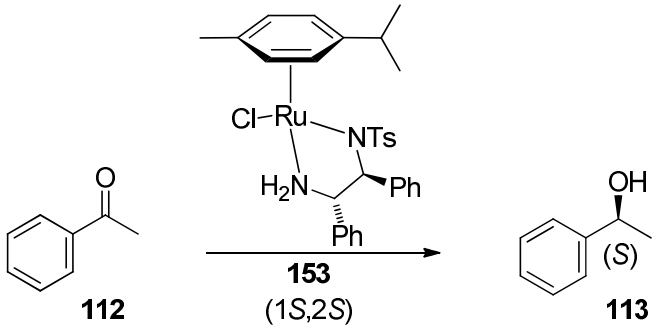


Figure 30: Equilibrium between Ru-formate complex **164** and Ru-hydrido complex **155**.

For more economical processes and green synthesis, there is an interest in using water as the solvent. Xiao has observed, that transfer hydrogenation using FA:TEA became much slower in water.[186] This interesting finding lead to use of sodium

formate as an efficient source of hydrogen for asymmetric transfer hydrogenation in water.



Scheme 11: Asymmetric transfer hydrogenation of acetophenone **112** with compound **153**.

Table 11: Asymmetric transfer hydrogenation of acetophenone **112** using compound **153** as catalyst with different hydrogen sources.

Hydrogen source	Catalyst loading	Solvent	Temp	Time	% Conv	% ee
IPA/KOH	200:1 (*S*,*S*)	IPA	r.t.	15 h	95	97(*S*)
FA:TEA (5:2)	200:1 (*S*,*S*)	-	28 ^{o}C	20 h	>99	98(*S*)
FA:TEA (5:2)	100:1 (*R*,*R*)	Water	40 ^{o}C	30 min	1	>99(*R*)
				12 h	98	97(*R*)
HCOONa	100:1 (*R*,*R*)	Water	40 ^{o}C	30 min	76	95(*R*)

The Ru-TsDPEN complex **153** was found to be very slow for the reduction of acetophenone using FA:TEA in water, on the other hand the reaction was much faster when carried out using sodium formate in water. Compound **153** gave 1% conversion and >99% ee for asymmetric transfer hydrogenation of acetophenone using FA:TEA (5:2) in water at 40 ^{o}C (Table 11). While under the similar conditions compound **153** gave 76% conversion and 95% ee in 30 min using sodium formate (Table 11).[187]

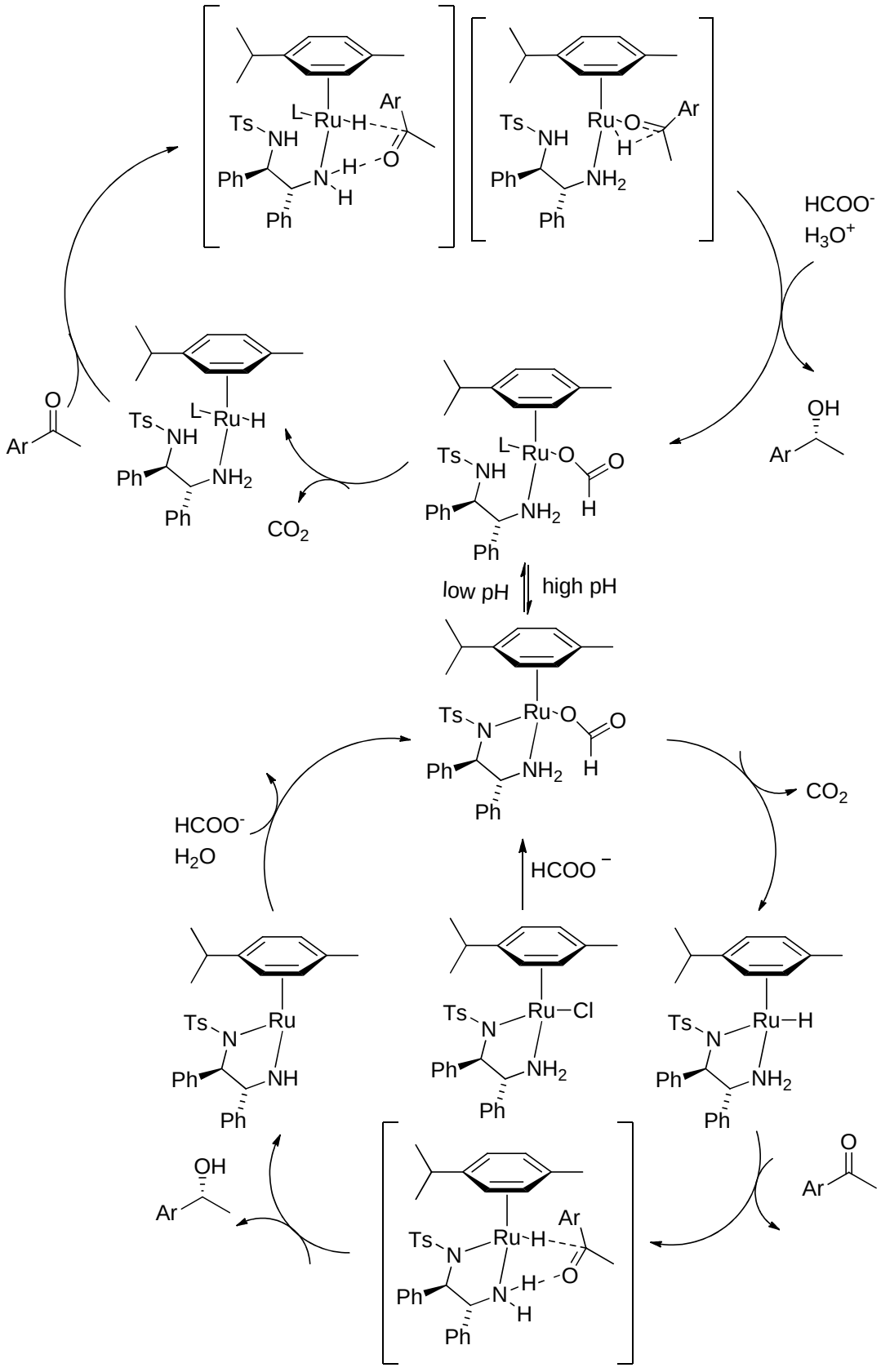


Figure 31: Mechanistic cycles in asymmetric transfer hydrogenation of aryl ketones in water at high and low pH.

To understand the asymmetric transfer hydrogenation in aqueous media, Xiao has reported the effect of pH on the catalytic cycle of transfer hydrogenation.[187] He has proposed that asymmetric transfer hydrogenation in aqueous media operates *via* two competing catalytic cycles as shown in Figure 31, which are dependent on the pH of the solution.[187] When the pH of the solution is low; the tosylated amine of the ligand gets protonated. This protonated form of the tosylated amine may lead to partial dissociation from the metal, with loss of rigidity in the complex (Figure 31).

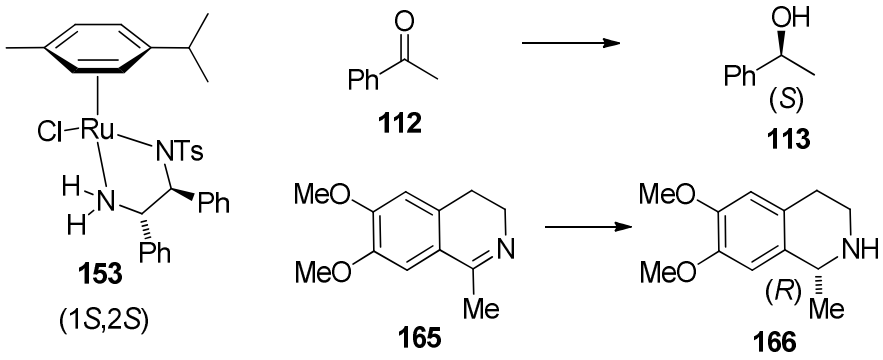
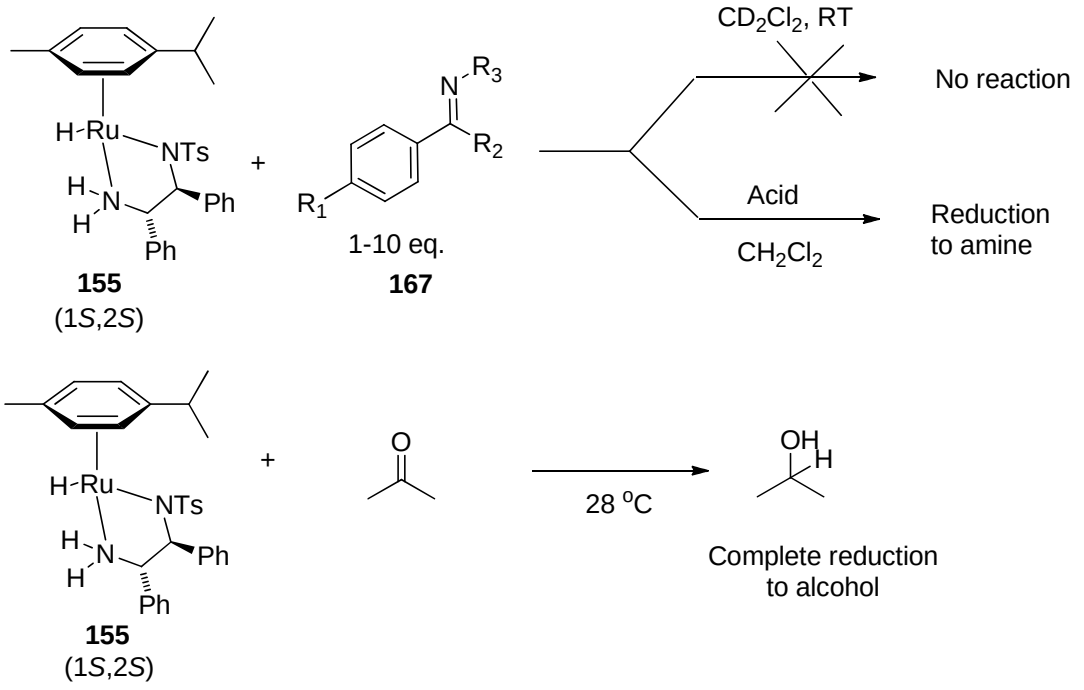


Figure 32: Asymmetric transfer hydrogenation of ketones and imines using complex (*1S,2S*)-**153**.

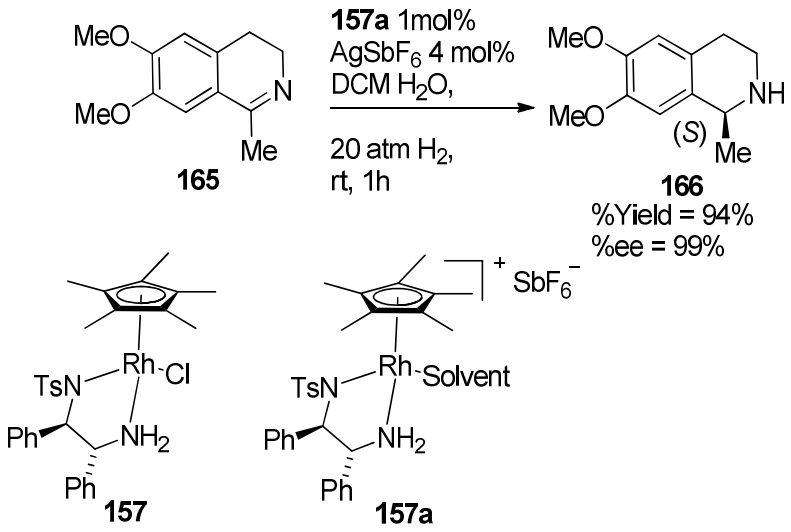
Due to this, the transfer hydrogenation is no longer enantioselective. Thus, if the pH of solution is adjusted to between 5-8 during the reaction by changing the ratio of formic acid/triethylamine, this can give rise to high efficiency and excellent enantioselectivities.[187]

One of the interesting findings to come from the transfer hydrogenation of ketones and imines, is that the use of the same configuration of chiral complex for ketone and imine reduction resulted in different product isomers (Figure 32).[173,188] The transition states for the corresponding imine reductions are less well understood, although there is evidence that the iminium salt, formed by protonation, rather than the free imine, is reduced.[189]



Scheme 12: Reaction of complex **155** (preformed hydride complex) with imines and ketones.

Bäckvall *et al*. have reported the experimental support for hydrogenation of imine by an ionic pathway.[190] They successfully carried out the reaction of acetone with preformed hydrido Ru complex **155** to give alcohol, and at the same time the similar reaction of hydrido complex **155** with imine **167** was unsuccessful (Scheme 12). Moreover, even when the stoichiometric reaction of hydrido complex **155** with imine **167** was carried out in 1:1 ratio, transfer hydrogenation to give an amine was not observed (Scheme 12).[190] The stoichiometric reaction carried out with addition of acid successfully resulted in formation of the amine product. This experimental data clearly shows that imine reduction follows an ionic pathway in asymmetric transfer hydrogenation and a source of protons is required to give reduction of the imine, which may be from the solvent or by addition of an acid; in the case of FA/TEA as solvent, the formic acid can supply the protons.[190]



Scheme 13: Reduction of imine **165** using compound **157**.

Xiao and Li have reported the asymmetric hydrogenation of imines using compound **157** with a range of counteranions.[191a] Out of the silver salts used, $AgSbF_6$ has given the highest conversion (94%) and highest selectivity (99% ee) for the asymmetric hydrogenation of imine **165**. Thus, the ionic nature of compound **157a** with a large counteranion (SbF_6^-) was found to be important for asymmetric hydrogenation for a range of substituted imines.[191a] The addition of the silver salts gave high conversions and enantioselectivities for the asymmetric pressure hydrogenation[191a] and asymmetric transfer hydrogenation[191b] of imines. To study the effect of the counteranion, Xiao *et al*. have reported the use of phosphate anions with Cp*Ir complexes for asymmetric hydrogenation of acyclic imines.[192,193] Ikariya *et al*. have also reported the use of $AgSbF_6$ with compound **160** for efficient and selective asymmetric hydrogenation of acyclic imines.[194]

Wills *et al*. have also reported similar results and speculated the orientation for the imine reduction shown in Figure 33.[194] For asymmetric transfer hydrogenation of imines, three different orientations are possible as shown in Figure 33. If the

orientation of imine **165** is similar to that of acetophenone **112**, the result will be reduction to the imine of incorrect configuration (Figure 33, B). Two orientations C & D exist (Figure 33), which will furnish the correct configuration of the product amine. However, it is difficult to firmly identify the exact orientation of the catalyst and imine during the transfer hydrogenation.[194] Kačer *et al*. described molecular modelling data of the transition states involved in asymmetric transfer hydrogenation of ketones and imines, which can help to explain the experimental data obtained.[195]

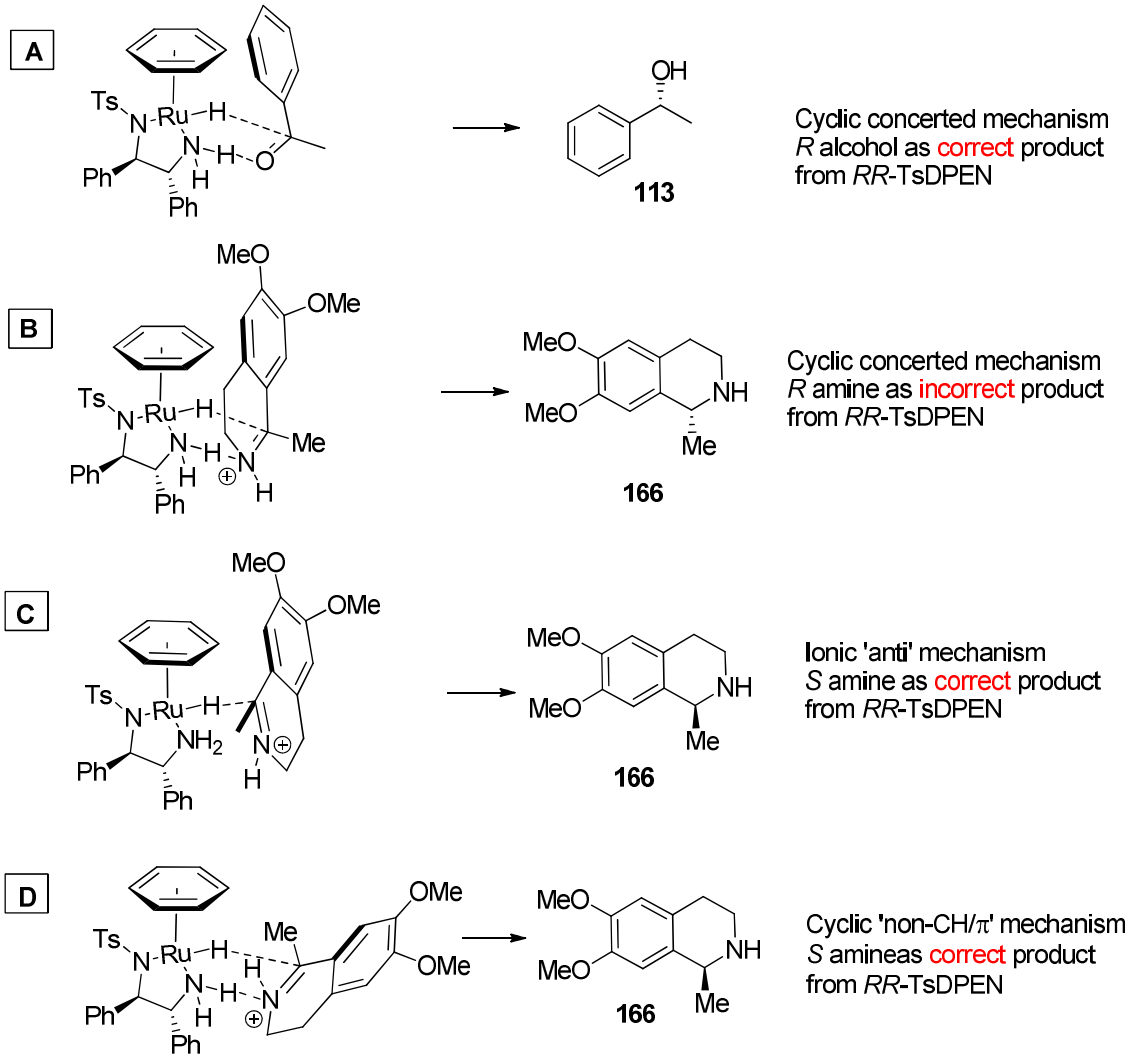


Figure 33: Established (A) and speculated (B-D) transition states for asymmetric transfer hydrogenation of ketones and imines using TsDPEN-Ru catalyst.

1.4.5 Factors affecting Enantioselectivity

In asymmetric transfer hydrogenation, the stable complex **153** has been used, which can be easily prepared *in situ* or isolated by reaction of $[Ru(arene)Cl_2]_2$ with chiral ligands such as TsDPEN. Complex **153** is a precatalyst, as during the reaction it is converted into the 16 electron species **154** by reaction with KOH in toluene. The 16 electron species reacts with IPA to give the hydride form of the catalyst **155.**[176]

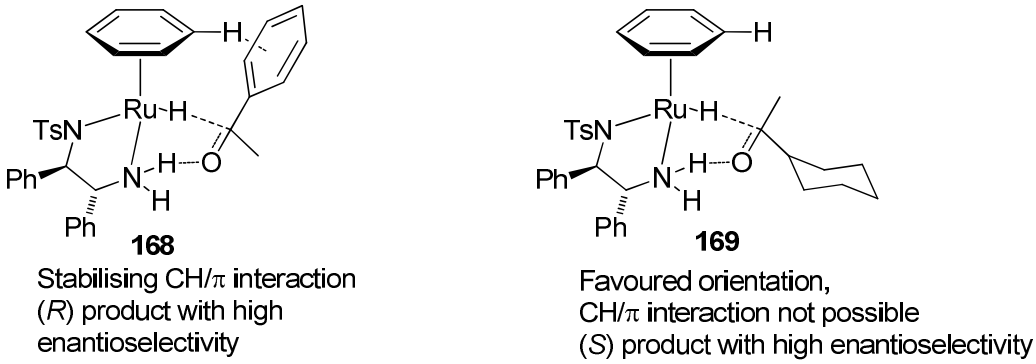


Figure 34: CH/π interaction in asymmetric transfer hydrogenation of ketones.

The enantioselectivity may arise due to a stereodetermining transition state with electronic influences around the metal centre and also *via* space interactions between the catalyst and substrate. The transition state structure was studied by hybrid density functional theory-based calculations for compound **155**. This study has revealed that enantioselectivity originates not only from the well-defined cyclic transition state but also through a CH/π interaction of η^6-arene of the complex and the aryl group of the substrate as shown in Figure 34.[197-198]

Andersson *et al*. also reported the DFT calculation for three different mechanistic models for the asymmetric transfer hydrogenation with Ru(arene)-aminoalcohol, (**A**) direct transfer of an R-hydrogen of an alcohol to the carbonyl carbon of a ketone, (**B**) migratory insertion (MI) of a coordinated ketone into a metal hydride bond, or (**C**) a

concerted mechanism where a proton and a hydride are transferred simultaneously to the ketone (Figure 35).[199] The computational data has shown that the six membered transition state has a strong preference for planarity. The planarity of the transition state is also dependent on the conformational behavior of the O,N-linkage of the amino alcohol ligand.[199]

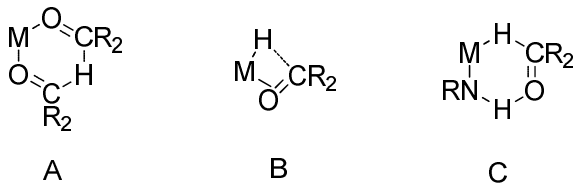


Figure 35: Possible model for transfer hydrogenation between metal hydride and ketones.

In 2004, Brandt, Roth and Andersson reported more experiments which provide an insight into the asymmetric transfer hydrogenation of ketones.[200] They reported asymmetric transfer hydrogenation of different substituted aliphatic and aromatic ketones and used these data for DFT calculations. Both experimental and computational data were found which provided additional support for the interaction between the substrate phenyl ring and metal arene ring, which is in contrast to aliphatic ketones. At the same time, enantioselectivity in transfer hydrogenation of ketones is also influenced by steric, electrostatic, dispersion and solvent effects.[200] As a result, excellent enantiomeric excesses are observed for substrates containing a combination of aryl and alkyl substituents on the carbonyl group. For substrates not fitting this model, enantioselectivities are frequently lower and unpredictable, although there are examples of alternative asymmetric transfer hydrogenation catalysts which have a broad substrate range.[200]

1.4.6 Recent Developments

The Wills group reported the first example of a "tethered" catalyst, where the chiral ligand and arene ring are joined together in the metal complex (Figure 36).[201-203] The introduction of the tethering linkage allows 'locking' of the otherwise freely rotating arene ring. The restriction of the metal-arene rotation subsequently permits the addition of substituents on the arene ring, which will occupy fixed spatial positions in the catalyst. Moreover, the three point attachment of ligand to the metal can give more stability.[201]

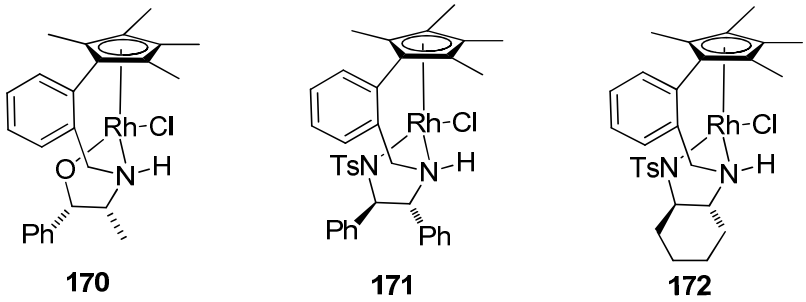
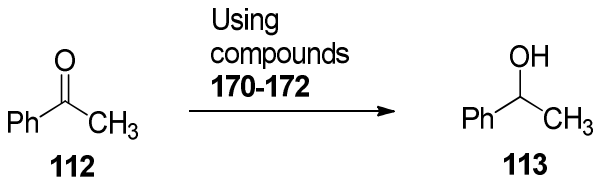


Figure 36: Cp*Rh-tethered complexes.

Compound **170** gave almost 50% conversion in 10 min at room temperature with S:C = 100:1, while almost 95% conversion was obtained in 10 min with S:C = 100:5, whilst over the period of the reaction a decrease in ee was observed (Table 12). This may be due to the low stability of the complex leading to racemisation of complex in the reaction.[201] In 2005 the Wills group reported a stable complex of Rh-metal, compound **171**.[202] Compound **171** gave complete conversion with 98% ee for asymmetric transfer hydrogenation of acetophenone in FA:TEA (Table 12). Compound **171** was also found to be highly efficient and enantioselective for a range of aryl alkyl ketones.[202]



112 **113**

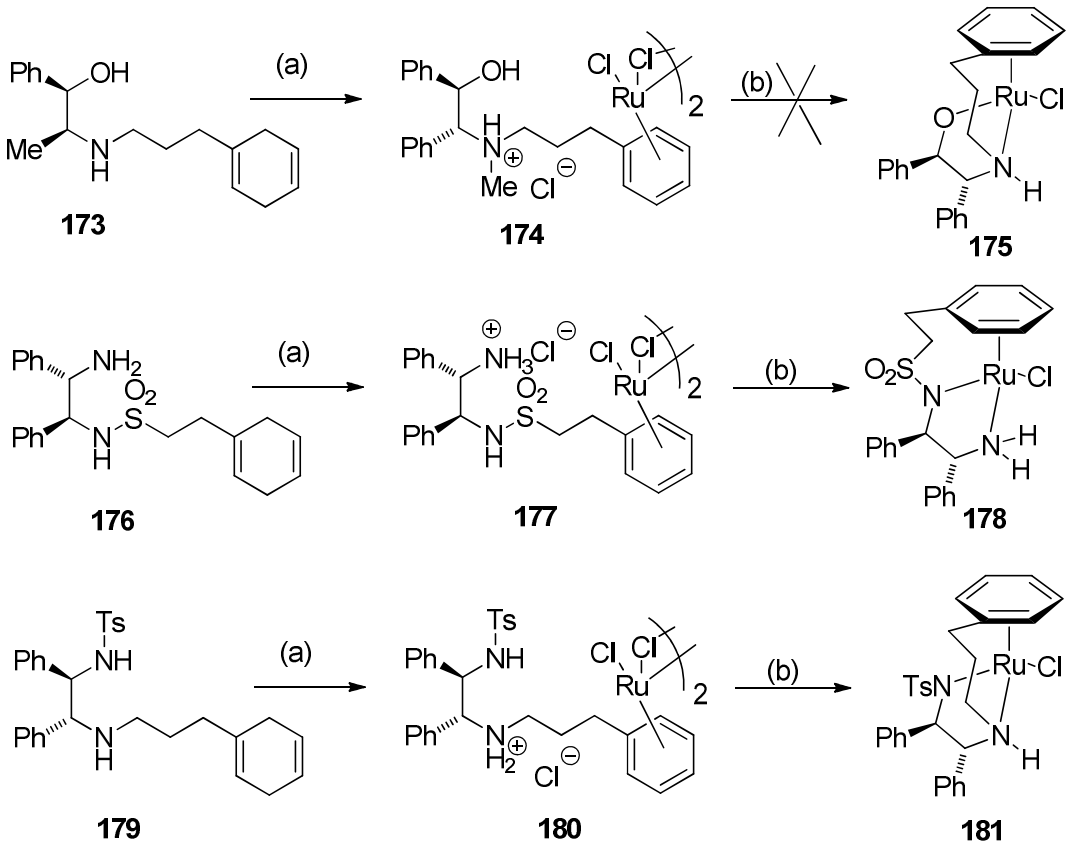
Table 12: Asymmetric transfer hydrogenation of acetophenone **112** using complexes **170**-**172**.

Compd	Hydrogen source	S/C	Solvent	Temp	Time	% Conv	% ee
					1 min	18.5	74.9 (*R*)
170	IPA/KO^{t}Bu	100	IPA	r.t.	10 min	50.4	68.6(*R*)
					60 min	62.1	55.8(*R*)
					1 min	78.2	73.5(*R*)
170	IPA/ KO^{t}Bu	20	IPA	r.t.	10 min	95.0	68.0(*R*)
					60 min	96.4	64.2(*R*)
171	FA:TEA	200		25 ^{o}C	10 h	100	98 (*R*)
172	FA:TEA	200		28 ^{o}C	2 h	100	96 (*R*)
172	HCOONa/H_2O	200		28 ^{o}C	3 h	100	96 (*R*)

A similar compound with a TsCYDN chiral core, compound **172** has been reported by the same group.[203] Compound **172** showed high activity, giving complete conversion in 2h for asymmetric transfer hydrogenation of ketones in FA:TEA with enantioselectivities of up to 96% ee at 28 ^{o}C (Table 12). Compound **172** gave similar results for various ketones tested. Moreover, compound **172** has shown similar catalytic activity with sodium formate in water as the hydrogen donor.[203]

In 2004-2005, the Wills group reported a series of tethered catalysts containing a chiral core derived from TsDPEN or a diphenyl aminoalcohol linked to the arene and Ru complex.[204-205] The synthesis of these complexes is now well established (Scheme 14). The chiral ligands can be synthesised by reductive amination of the

appropriate aldehyde and amine. The resulting ligands were reacted with $RuCl_3$ to give the corresponding dimer. The dimer can usually be converted into a monomer complex under basic conditions (Scheme 14).[204-205]



Reagents and Conditions: (a) HCl (2M in Et_2O), dry DCM, 15 min; $RuCl_3.3H_2O$, EtOH, 78 °C, 21 h; (b) NEt_3, IPA, 80 °C, 1 h.

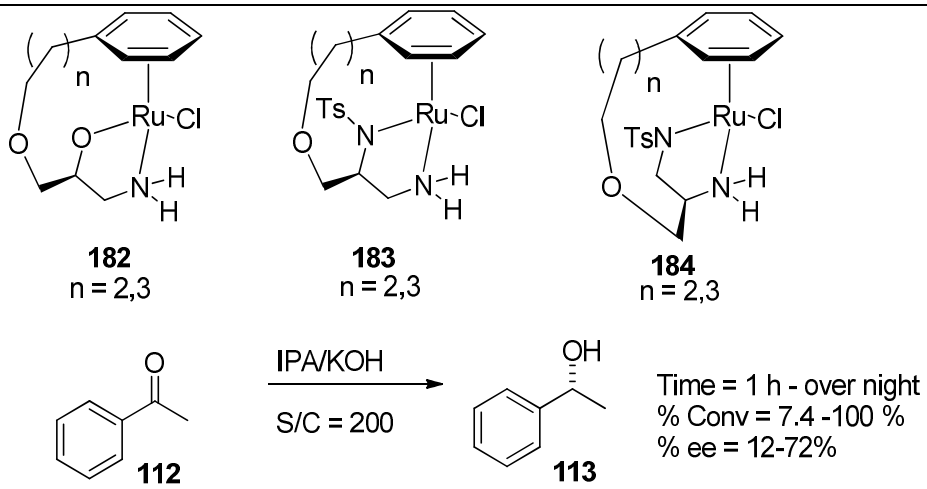
Scheme 14: Synthesis of different Ru-tethered complexes.

Under these conditions compound **174** failed to give compound **175**, however the dimer itself can be used directly for asymmetric transfer hydrogenation, as during the reaction it converts to the monomer *in situ*. The results obtained by the dimer and isolated monomer for asymmetric transfer hydrogenation are shown in Table 13.[204-205] Compound **174** gave 96% conversion for transfer hydrogenation of acetophenone with moderate enantioselectivity of 66% in IPA/KOH (Table 13).[204] Compound **177** and the corresponding monomer **178** have shown similar high activity with >99%

conversion and high enantioselectivity of up to 96% ee in FA:TEA at 28 ^{o}C in 18-20 h (Table 13).[205] Interesting results were obtained with dimer **180** and corresponding monomer **181**. Both compounds **180** and **181** were found to be highly active and efficient for acetophenone reduction with 100% conversion within 3 h and 96% ee being obtained using FA:TEA (Table 13).[205]

Table 13: Asymmetric transfer hydrogenation of acetophenone **112** using complexes **174**, **177**, **178**, **180** and **181**.

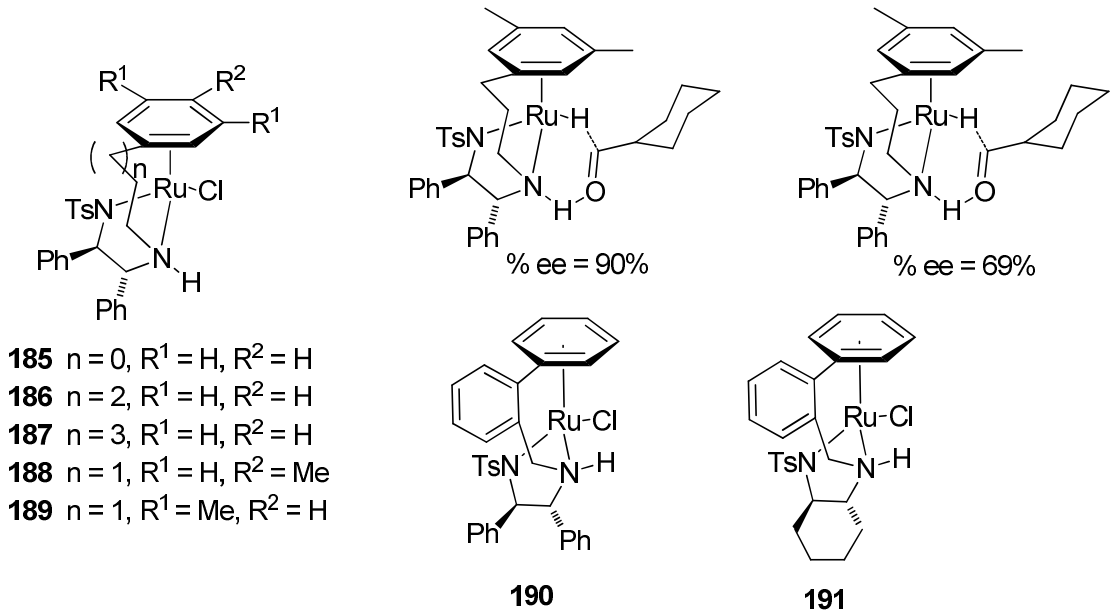
Compd	Hydrogen source	S/C	Temp	Time	% Yield	% ee
174	IPA/KOH	200	28 ^{o}C	1 h	96	66(*R*)
177	FA:TEA	200	28 ^{o}C	18 h	>99	96(*R*)
178	FA:TEA	200	28 ^{o}C	21 h	>99	96(*R*)
180(*S*,*S*)	FA:TEA	100	28 ^{o}C	3 h	100	96(*S*)
181(*R*,*R*)	FA:TEA	100	28 ^{o}C	3 h	100	96(*R*)



Scheme 15: Modified tethered catalyst analogues with ether linkage.

Modified tethered complexes, with ether linkages in the chain was reported by Wills *et al*.[206] Compounds **182**-**184** with ether linkages and different chiral cores with Ru complex, were studied for asymmetric transfer hydrogenation of acetophenone (Scheme 15).[206] All of them showed comparable efficiency for conversion, but enantioselectivities were moderate and in the range of 12-72% ee.

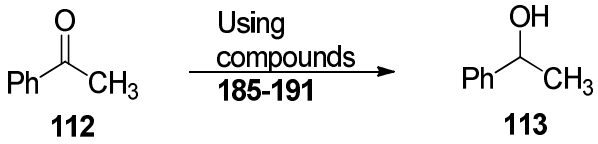
At the same time the variation in the length of the tether in the complex has been studied by the same group (Figure 37).[207] Compound **185** with "2C" tether length has shown low reactivity compared to the "3C" analogue (Table 14). Compounds **188** and **189** with the "3C" in the tether length with methyl substitution, gave a comparable results for asymmetric transfer hydrogenation of acetophenone with 38% conversion and 93-96% ee in 4-5 h at 40 ^{o}C, but were not as good as the "4C" analogue **186** with 100% conversion and 96% ee under similar reaction conditions (Table 14).[207] Compound **186** gave a very fast reaction, giving complete conversion in 1.25 h at 28 ^{o}C with 96% ee.



185 n = 0, R^1 = H, R^2 = H
186 n = 2, R^1 = H, R^2 = H
187 n = 3, R^1 = H, R^2 = H
188 n = 1, R^1 = H, R^2 = Me
189 n = 1, R^1 = Me, R^2 = H

190 **191**

Figure 37: Modified tethered analogues with change in linkage.



112 **113**

Table 14: Asymmetric transfer hydrogenation of acetophenone **112** using complexes **185**-**191**.

Compd	Hydrogen source	S/C	Temp	Time	% Yield	% ee
185 "2C"	FA:TEA	200	40 ^{o}C	15 h	19	92 (*R*)
186 "4C"	FA:TEA	200	40 ^{o}C	1.5 h	100	96 (*R*)
186 "4C"	FA:TEA	10000	r.t.	70 h	100	96 (*R*)
187 "5C"	FA:TEA	200	40 ^{o}C	6 h	38	94(*R*)
188	FA:TEA	200	40 ^{o}C	4 h	38	96(*R*)
189	FA:TEA	200	40 ^{o}C	5 h	38	93(*R*)
190	FA:TEA	200	40 ^{o}C	24h	100	98(*R*)
191	FA:TEA	200	28 ^{o}C	12 h	100	92(*R*)

Moreover, compound **186** can be used up to 0.01 mol% catalyst loading for acetophenone reduction to give complete conversion in 70 h with intact enantioselectivity (96% ee) (Table 14).[207] Interestingly, compound **189** has shown high enantioselectivity (90% ee) for asymmetric transfer hydrogenation of cyclohexylmethyl ketone with complete conversion in an overnight reaction.[207]

Compound **190** with benzene in the tether, also gave similar results for acetophenone reduction with complete conversion in 24 h at 40 ^{o}C and high enantioselectivity of 98% ee (Table 14).[208] The TsCYDN analogue compound **191** was found to be less active compared to **153** (TsDPEN analogue) with complete conversion in 12 h at 28 ^{o}C, but enantioselectivity was only 92% ee (Table 14).[208]

The Wills group have reported various *N*-alkylated TsDPEN derivatives **192a-e** as chiral ligands for pressure hydrogenation with $IrCl_3$ in presence of base for different ketones (Figure 38).[209] These *N*-alkylated TsDPEN chiral ligands **193a-e** were also used for Ru complex catalysed asymmetric transfer hydrogenation of different aryl alkyl ketones and imines (Figure 38).[195,210] Compound **193a** with *N*-Me has shown high efficiency and high selectivity for acetophenone reduction compared to its -NH_2 analogue (Scheme 16).[210]

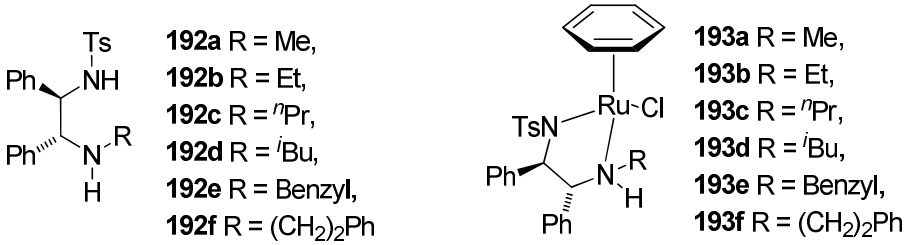
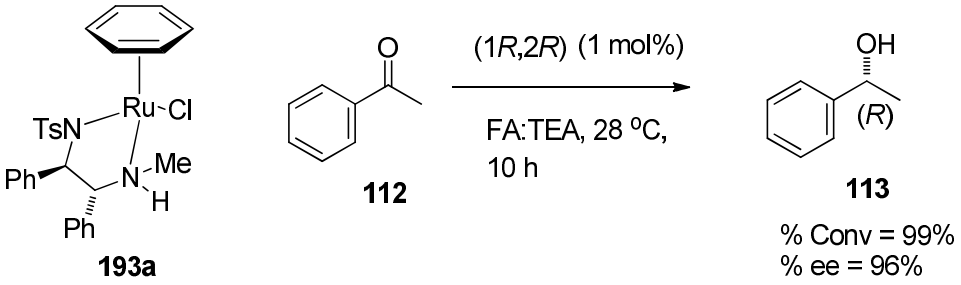


Figure 38: *N*-alkylated TsDPEN derivatives.



Scheme 16: Asymmetric transfer hydrogenation of acetophenone using complex **193a** using FA:TEA.

Recently, different chiral ligands have been reported by various groups for asymmetric transfer hydrogenation of ketones. Govender *et al*. have reported that tetrahydroisoquinoline diamine compound **194**, gave 81% conversion for acetophenone reduction using $[RhCp^*Cl_2]_2$ in IPA/KO^{t}Bu at 25 ^{o}C with moderate enantioselectivity of 70% ee (Figure 39, Table 15).[211]

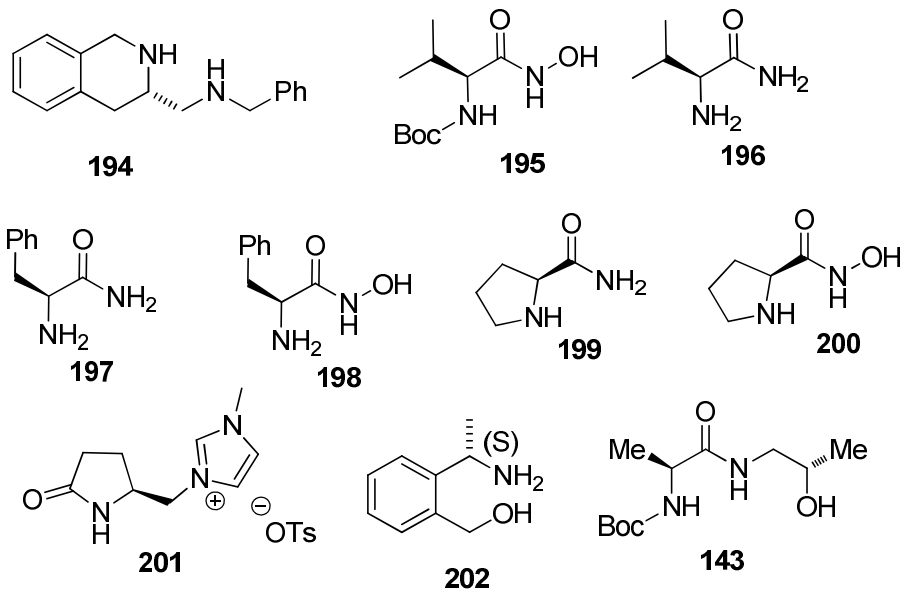
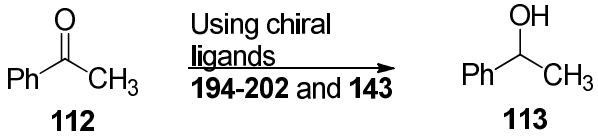


Figure 39: Recently developed chiral ligands for asymmetric transfer hydrogenation of ketones.

Ahlford and Adolfsson have reported a series of amino acid derived amide and hydroxamic acid derivatives **195-200** as ligands for asymmetric transfer hydrogenation using $[IrCp^*Cl_2]_2$ in $HCOOLi/H_2O$ (Figure 39).[212] Compound **195** (-*N*HBoc) gave a very low conversion of 2% for the reduction of acetophenone under reaction conditions. While deprotected compound **196** gave a high conversion of 99% with a moderate ee of 71% in combination with $[IrCp^*Cl_2]_2$. Similar analogues **197-200** were found to be good in terms of conversion but the enantioselectivity was poor with $[RhCp^*Cl_2]_2$ or $[IrCp^*Cl_2]_2$ (Table 15).[212]

Vo-Tanah has reported chiral *N*-heterocyclic carbene derivatives of (*S*)-pyroglutamic acid as chiral ligands for Rh catalysed asymmetric transfer hydrogenation.[213] In this series, compound **201** was found good with 90% conversion and 80% ee achieved at 80 ^oC in 20 h for asymmetric transfer hydrogenation for acetophenone with $[Rh(COD)Cl_2]_2$.[213]



112 **113**

Table 15: Asymmetric transfer hydrogenation of acetophenone **112** using chiral ligands **194-202** and **143**.

Compd	Metal	Hydrogen source	S/C	Temp	Time	% Yield	% ee
194	$[RhCp^*Cl_2]_2$	IPA/KO^{t}Bu/ H_2O	100	25 ^oC		81	70(*S*)
195	$[RhCp^*Cl_2]_2$	HCOOLi/ H_2O	100	28 ^oC	17-22 h	2	-
196	$[IrCp^*Cl_2]_2$	HCOOLi/ H_2O	100	24 ^oC	17-22 h	99	71(*R*)
197	$[IrCp^*Cl_2]_2$	HCOOLi/ H_2O	100	28 ^oC	17-22 h	99	43(*R*)
198	$[RhCp^*Cl_2]_2$	HCOOLi/ H_2O	100	28 ^oC	17-22 h	99	29(*R*)
199	$[RhCp^*Cl_2]_2$	HCOOLi/ H_2O	100	35 ^oC	17-22 h	99	76(*R*)
200	$[IrCp^*Cl_2]_2$	HCOOLi/ H_2O	100	24 ^oC	17-22 h	99	74(*R*)
201	$[Rh(COD)Cl_2]_2$	IPA/KOH	50	80 ^oC	20 h	90	80(*R*)
202	$[Ru(p\text{-cymene})Cl_2]_2$	IPA/KOH	200	-10 ^oC	3 h	98	92(*R*)
143 (S)	$[Ru(p\text{-cymene})Cl_2]_2$	EtOH/LiCl	100	40 ^oC	2 h	83	97(*S*)

Zheng *et al*. have reported a series of amino alcohol ligands derived from 1-phenylmethylamine.[214] Promising results were obtained with compound **202** (Figure 39, Table 15). Compound **202** gave 98 % conversion with good enantioselectivity of 92% ee using $[Ru(p\text{-cymene})Cl_2]_2$ in IPA/KOH at -10 ^oC in 3 h for transfer hydrogenation of acetophenone.[214]

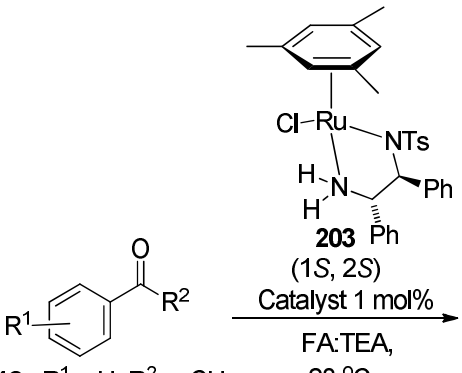
A more interesting result was reported by Adolfsson *et al*. using compound **143**.[215] Compound **143** has been reported by this group for asymmetric transfer hydrogenation of ketones using [Ru(*p*-cymene)Cl_2]$_2$ and IPA/NaOH.[171] Compound **143** has been found to be effective in Ru catalysed asymmetric transfer hydrogenation using EtOH/LiCl (Table 15).[215] Compound **143** gave 83% conversion with high 97% ee with [Ru(*p*-cymene)Cl_2]$_2$ for transfer hydrogenation of acetophenone at 40 ^{o}C in 2 h, with 90% chemoselectivity (due to side reaction of acetophenone and acetaldehyde).

1.4.7 Substrate scope

There is a large range of substrates that can be employed for asymmetric transfer hydrogenation reactions especially (i) important substrates for biologically active compounds and (ii) compounds which are structurally interesting and challenging. A selection of these substrates is described in this section with highlights of some of the applications of biologically relevant compounds.

1.4.7.1 Aryl Alkyl Ketones

A number of the chiral ligands and complexes have shown high efficacy and selectivity for transfer hydrogenation of various aryl alkyl ketones as discussed in sections 1.4.3 and 1.4.6. Compound **203** has shown high selectivity for a range substituted ketones (Scheme 17, Table 16). For all tested compounds complete conversion was obtained in 14-90 h using complex **203** with high enantioselectivity.[173]



112 R^1 = H, R^2 = -CH_3
204a R^1 = m-Cl, R^2 = -CH_3
204b R^1 = p-Cl, R^2 = -CH_3
204c R^1 = p-CN, R^2 = -CH_3
204d R^1 = m-OCH_3, R^2 = -CH_3
204e R^1 = p-OCH_3, R^2 = -CH_3
204f R^1 = -H, R^2 = -C_2H_5
204g R^1 = -H, R^2 = -$(CH_2)_3CO_2Et$

113 R^1 = H, R^2 = -CH_3
205a R^1 = m-Cl, R^2 = -CH_3
205b R^1 = p-Cl, R^2 = -CH_3
205c R^1 = p-CN, R^2 = -CH_3
205d R^1 = m-OCH_3, R^2 = -CH_3
205e R^1 = p-OCH_3, R^2 = -CH_3
205f R^1 = -H, R^2 = -C_2H_5
205g R^1 = -H, R^2 = -$(CH_2)_3CO_2Et$

Scheme 17: Asymmetric transfer hydrogenation of ketones using complex **203**.

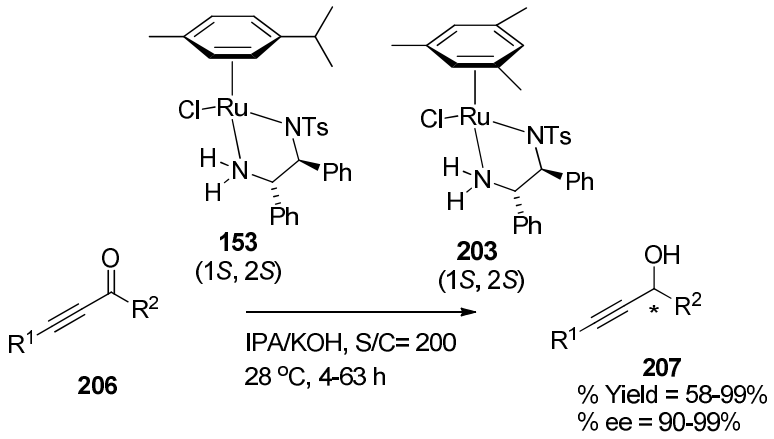
Table 16: Asymmetric transfer hydrogenation of ketones using complex **203**.

Ketone	Time	%conv	%ee	Ketone	Time	%conv	%ee
112	20 h	>99	98	**204d**	50 h	>99	98
204a	21 h	>99	97	**204e**	60 h	>99	97
204b	24 h	>99	95	**204f**	60 h	96	97
204c	14 h	>99	90	**204g**	90 h	99	95

1.4.7.2 α,β-Acetylenic Ketones

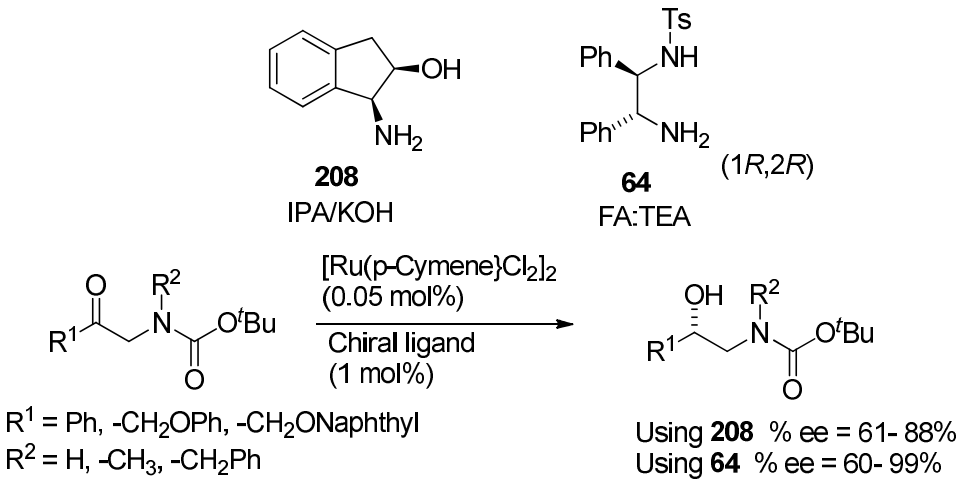
Asymmetric transfer hydrogenation of α,β-acetylenic ketones has been obtained using compounds **153** and **203** (Scheme 18).[216] Compounds **153** and **203** were found to be highly efficient (58-99% conversion) and enantioselective (90-99% ee) for asymmetric transfer hydrogenation of α,β-acetylenic ketones **206** to the corresponding chiral propargylic alcohols **207**.[216] In contrast, pressure hydrogenation of these compounds was less chemoselective and enantioselective due to conjugative

reduction. Compound **203** was found to be effective for asymmetric transfer hydrogenation of this series of compound in IPA, whereas demonstrated lower activity when used in FA:TEA.[216]



Scheme 18: Asymmetric transfer hydrogenation of α,β-acetylenic ketones.

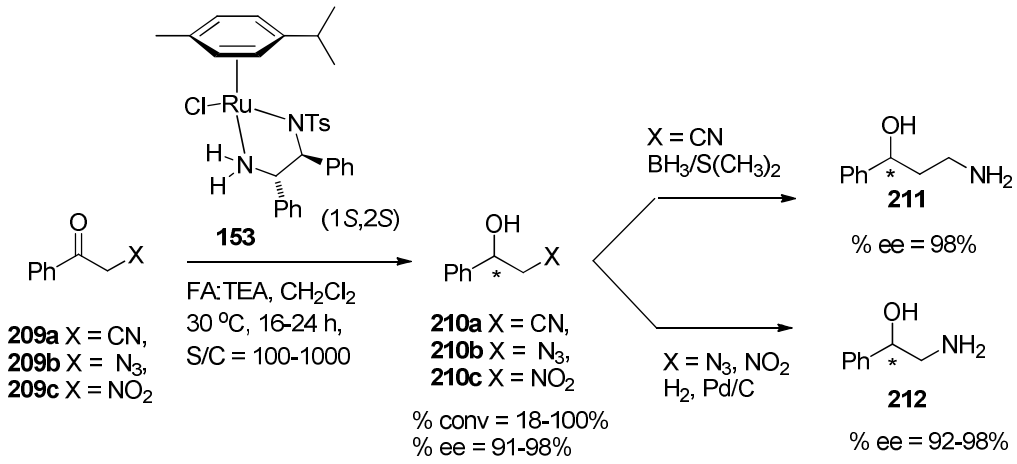
1.4.7.3 *α*-Substituted Ketones



Scheme 19: Asymmetric transfer hydrogenations of α-amino ketones.

Asymmetric transfer hydrogenations of α-amino ketones have been reported by the Wills group using compounds **208** and **64** in combination with [Ru(*p*-cymene)Cl_2]$_2$ (Scheme 19).[208,217] Compound **208** was found to be highly enantioselective, giving products of 60-99% ee for different α-substituted ketones with [Ru(*p*-cymene)Cl_2]$_2$.

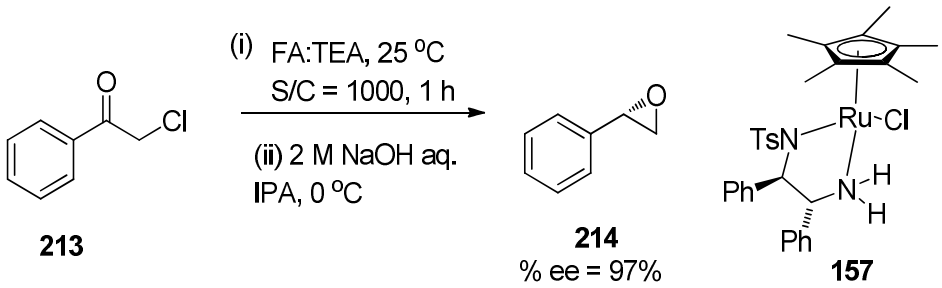
The resulting enantiopure alcohols can be employed for synthesis of enantioselective aziridines. [208,217]



Scheme 20: Asymmetric transfer hydrogenation of α-substituted ketones.

A similar application was reported by Ikariya in 2002 for asymmetric transfer hydrogenation of α-substituted ketones with groups such as -CN, N_3 and -NO_2 using compound **153** (Scheme 20).[218] Compound **153** gave a good efficiency (18-100%) and high enantioselectivity (91-98% ee) for transfer hydrogenation. The resulting -CN, N_3, -NO_2 substituted alcohols can be converted to optically pure amino alcohols by reduction.[218]

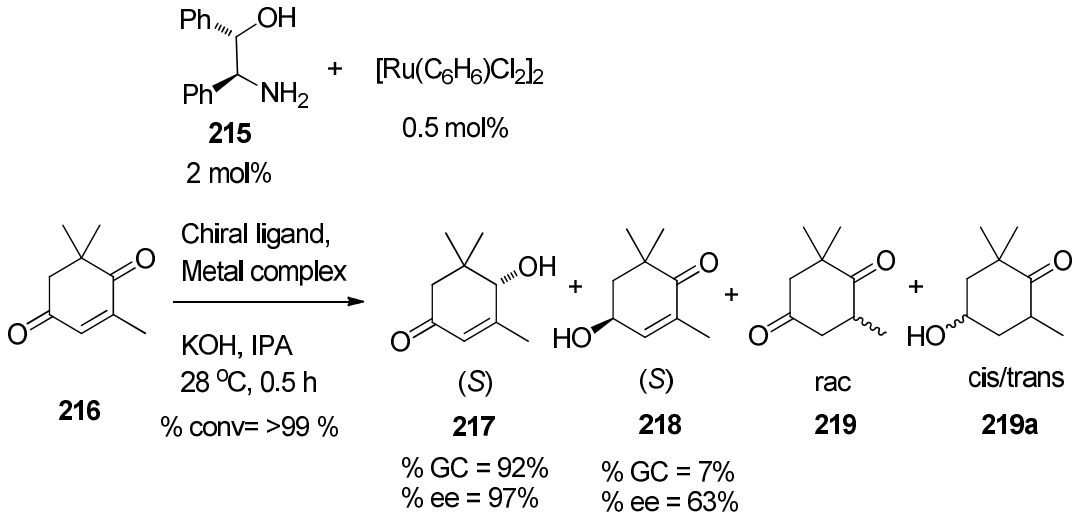
In the same year, Ikariya *et al*. reported the synthesis of optically active styrene oxides from 2-chloroacetophenones in a one-pot reduction-elimination procedure.[219] The first step was the enantioselective reduction of 2-chloroacetophenone using compound **157** giving 97% ee in FA:TEA and the resulting 2-chloro-1-phenylethanol converted to optically active styrene oxide **214** using 2M NaOH solution in isopropanol in 2 h (Scheme 21). This one-pot process is quite useful and economical for large-scale production of styrene oxides.[219]



Scheme 21: Asymmetric transfer hydrogenation of α-chloro ketones.

1.4.7.4 α,β-Unsaturated ketones

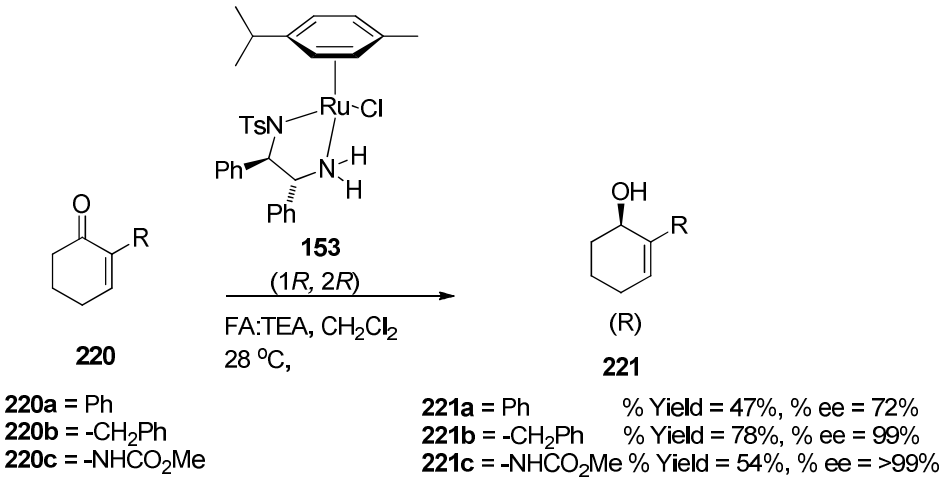
Püntener *et al*. reported asymmetric transfer hydrogenation of ketoisophorone **216** using *in situ* formed catalysts with different chiral ligands and $[Ru(C_6H_6)Cl_2]_2$ in IPA/KOH (Scheme 22).[220] Compound **215** in combination with $[Ru(C_6H_6)Cl_2]_2$ has shown high diastereoselectivity dr = 92:7 and high enantioselectivity (97% ee) for asymmetric transfer hydrogenation of compound **216**.[220]



Scheme 22: Asymmetric transfer hydrogenation of ketoisophorone.

Similarly, different chiral compounds have been employed by the Wills group for asymmetric transfer hydrogenation of α,β-unsaturated ketones using compound **153**

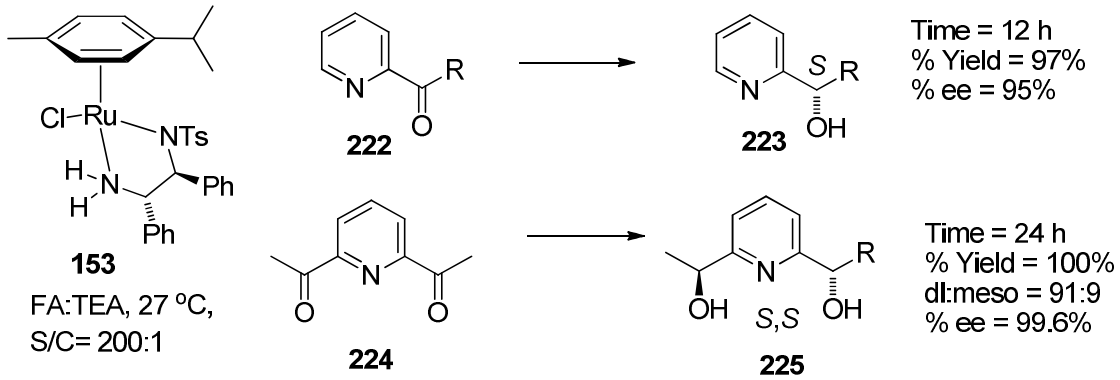
as the catalyst (Scheme 23).[221] Substituted cyclic enones **220a-c** were reduced with yields in the range of 47-78% and good to high enantioselectivities.[221]



Scheme 23: Asymmetric transfer hydrogenation of cyclic enones.

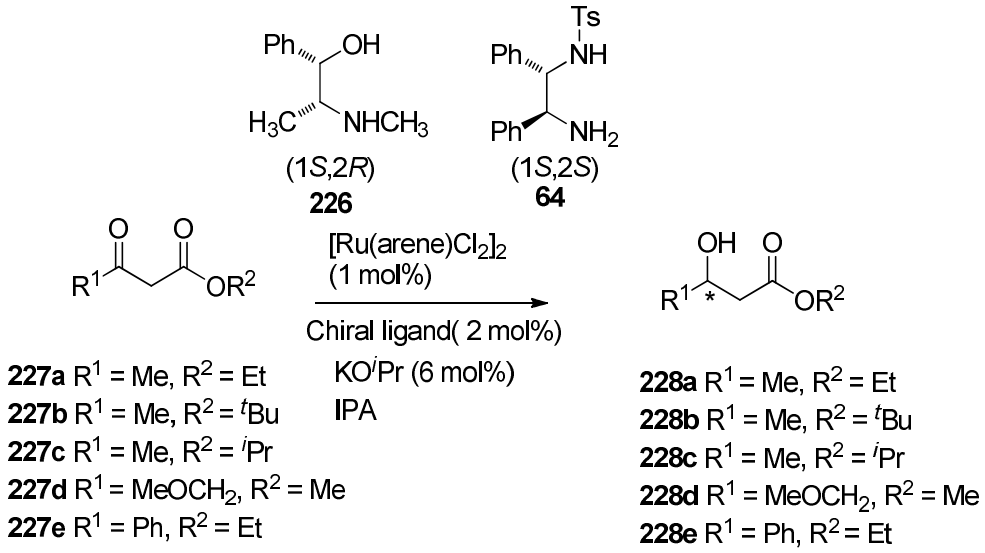
1.4.7.5 Heterocyclic ketones

Chiral heterocyclic alcohols are useful intermediates for synthesis of biologically active molecules, novel chiral ligands and natural products (Scheme 24). In 2000, Ikariya reported the reduction of 2-pyridyl alkyl ketone **222** using compound **153** with a high yield of up to 97% and high enantioselectivity of up to 95% ee using FA:TEA.[222] Interesting results were also obtained for compound **224**. The resulting symmetrical alcohol **225** can be converted to chiral ligands.[222]



Scheme 24: Asymmetric transfer hydrogenation of heterocyclic ketones.

1.4.7.6 β-Keto esters



Scheme 25: Asymmetric transfer hydrogenation of β-keto esters.

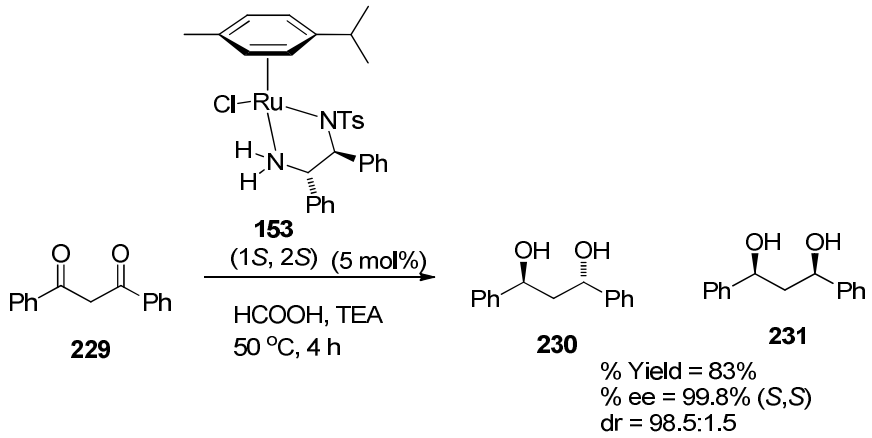
Table 17: Asymmetric transfer hydrogenation of β-keto esters.

Compd	Chiral ligand	Metal	Temp	Time	% Conv	% ee
227a	**226**	$[Ru(benzene)Cl_2]_2$	30 °C	10 h	100	39(*S*)
227a	**64**	$[Ru(hmb)Cl_2]_2$	50 °C	20 h	63	56(*R*)
227b	**226**	$[Ru(benzene)Cl_2]_2$	20 °C	1 h	98	44(*S*)
227c	**226**	$[Ru(benzene)Cl_2]_2$	20 °C	4 h	100	40(*S*)
227d	**226**	$[Ru(benzene)Cl_2]_2$	50 °C	2 h	100	15(*S*)
227e	**226**	$[Ru(p\text{-cymene})Cl_2]_2$	50 °C	15 h	85	94(*S*)
227e	**64**	$[Ru(p\text{-cymene})Cl_2]_2$	50 °C	3 h	95	93(*S*)

Transfer hydrogenation of β-keto esters was studied using ephedrine and TsDPEN with different Ru(arene) complexes by Carpentier (Scheme 25).[223] Different esters were studied by employing two chiral ligands; ephedrine **226** and TsDPEN **64** in combinations with different Ru(arene) complexes. Ephedrine **226** showed good

conversion but moderate enantioselectivity for asymmetric transfer hydrogenation of compounds **227a-d** in combination with Ru(arene) complexes. The best result was obtained for β-keto ester with an aryl substituent **227d**, using Ru(p-cymene)/Ephedrine **226** (85% conv and 94% ee) and Ru(p-cymene)/TsDPEN **64** (95% conv and 93% ee) (Table 17).[223]

1.4.7.7 1,3-Diketones



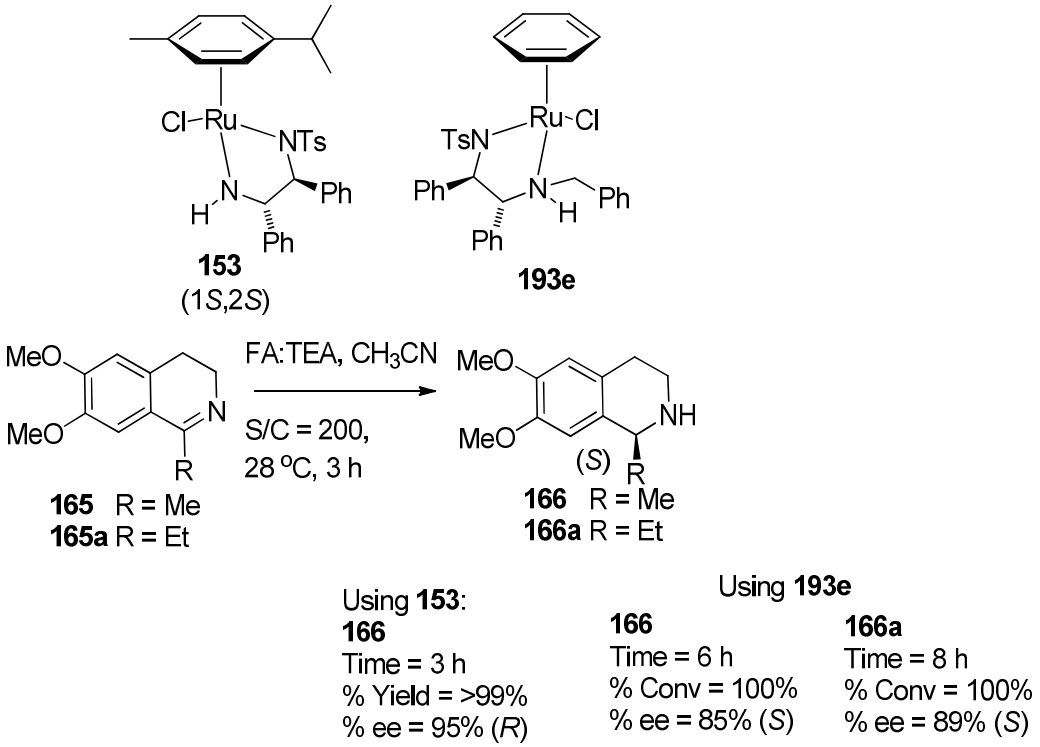
Scheme 26: Asymmetric transfer hydrogenation of 1,3-diketones.

Cossy *et al*. have reported asymmetric transfer hydrogenations of 1,3-diketones using chiral-Ru complexes (Scheme 26).[224] Compound **153** gave asymmetric transfer hydrogenation of compound **229** to give compound **230** with 83% conversion, 99.8% ee and dr of 98.5:1.5. Compound **153** also worked well for a range of substituted 1,3-diketones.[224]

1.4.7.8 Imines

Imines are important substrates for asymmetric transfer hydrogenation given the wide range of applications of enantiomerically pure amines. Noyori *et al*. reported high enantioselective and efficient transfer hydrogenation of imines using compound **153**.[188] Compound **165** was reduced to the corresponding amine **166** with more than

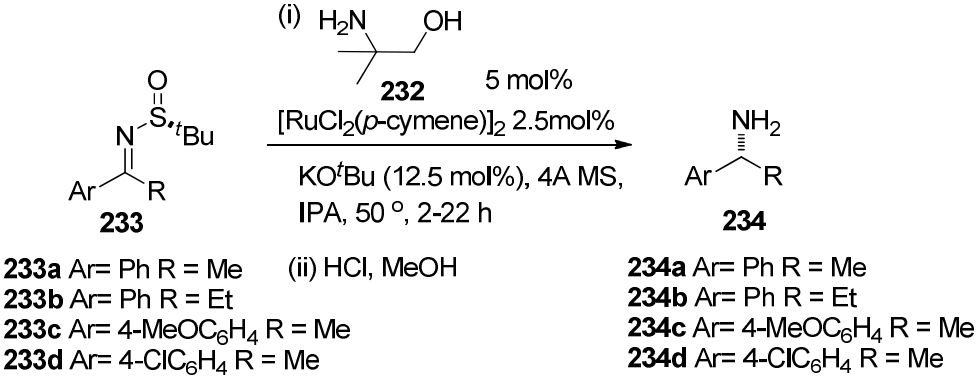
99% yield and 95% ee with compound **153** using FA:TEA as the hydrogen source in acetonitrile (Scheme 27). The transfer hydrogenation reaction was found to be very slow under neat conditions.[188] Similar results were obtained by the Wills group using compound **193e** (Scheme 27).[195] High enantioselectivity was obtained for the reduction of imines **165** and **165a** (85% and 89% ee respectively) using compound **193e**. [195]



Scheme 27: Asymmetric transfer hydrogenation of imines.

Recently, asymmetric transfer hydrogenation of sulfinylimines was reported by Guijarro using achiral amino alcohols and [Ru(*p*-cymene)Cl_2]$_2$ in IPA/KO^{t}Bu (Scheme 28).[225] Achiral ligands were screened for transfer hydrogenation of compound **233a**. The best result was obtained using compound **232** with [Ru(*p*-cymene)Cl_2]$_2$ at 40 ^{o}C in 4 h with 95% yield and 97% ee (Table 18).[225] Asymmetric transfer hydrogenation of different sulfinylimines **233b-d** was carried out under optimised conditions using compound **232** with [Ru(*p*-cymene)Cl_2]$_2$ to give products

of high optical purities in the range of 96-98% ee by diastereoselective reduction (Scheme 28). The sulfinyl group can easily be removed under mild acidic condition to give enantiomerically pure amine products.[225]



Scheme 28: Asymmetric transfer hydrogenation of sulfinylimines.

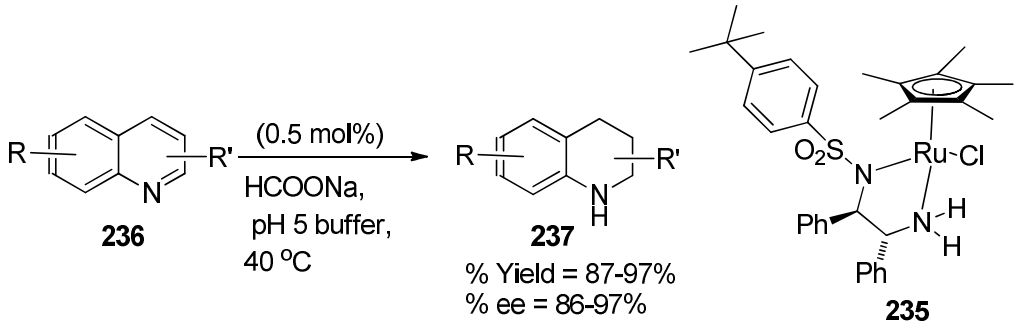
Table 18: Asymmetric transfer hydrogenation of sulfinylimines.

Compd	Temp	Time	% Conv	% ee
233a	50 °C	2 h	97	97
233b	50 °C	2 h	98	98
233c	50 °C	3 h	94	96
233d	50 °C	2.5 h	95	97
ent-233a	50 °C	2 h	96	98

1.4.7.9 Quinolines

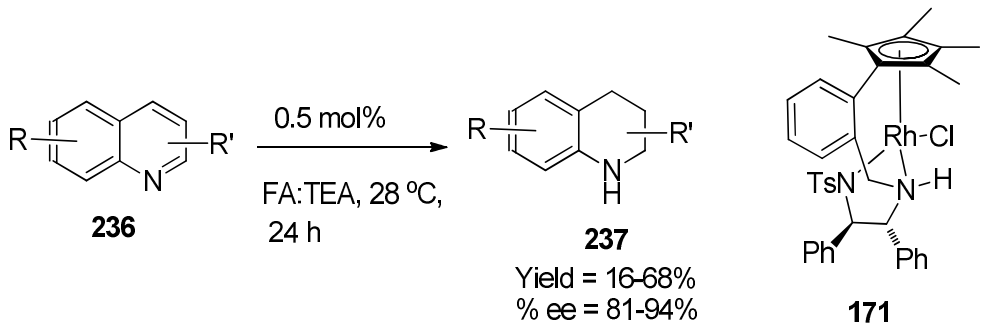
The first report on asymmetric transfer hydrogenation of quinolines was by Xiao in 2010.[226] 1,2,3,4-Tetrahydroisoquinoline is an important structural unit present in alkaloids, with applications in the drug and agrochemical industries. Compound **235** was identified as a promising catalyst for asymmetric transfer hydrogenation of 2-methyl quinoline using HCOONa/ buffer pH 5 at 40 °C to give high conversion

(96%) and high enantioselectivity of 97% ee (Scheme 29).[226] Compound **235** was employed for asymmetric transfer hydrogenation of differently substituted quinolines **236** under similar conditions to give tetrahydroquinolines **237** in high yields (87-97%) and with high enantioselectivities (86-97% ee).[226]



Scheme 29: Asymmetric transfer hydrogenation of quinolines.

Recently the Wills group has also reported the asymmetric transfer hydrogenation of quinolines using FA:TEA as hydrogen sources using Ru and Rh complexes.[227] Compound **171** gave comparable conversion and high enantioselectivity for a range of substituted quinolines using FA:TEA at 28 °C in 24 h (Scheme 30).[227]

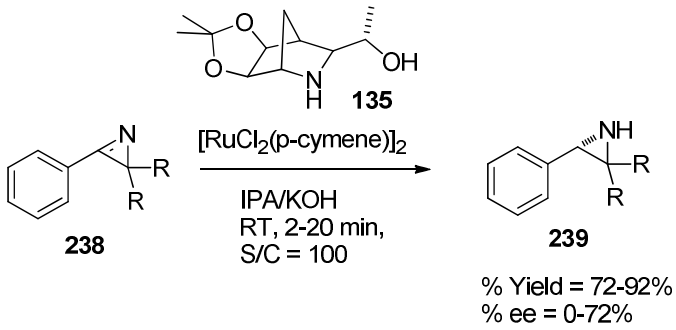


Scheme 30: Asymmetric transfer hydrogenation of quinolines.

1.4.7.10 Aziridines

Andersson *et al*. reported the enantioselective transfer hydrogenation of azirines **238** to chiral aziridines **239** with $[RuCl_2(p\text{-cymene})]_2$ using IPA/KOH.[228] Asymmetric

transfer hydrogenation of several azirine derivatives **238** was achieved in 2-20 min with good yields of 72-92% and enantioselectivities of 0-72% ee using chiral ligand **135** in combination with $[Ru(p\text{-cymene})Cl_2]_2$ (Scheme 31).[228]



Scheme 31: Asymmetric transfer hydrogenation of azirines.

1.4.8 Greener approaches to asymmetric transfer hydrogenation

To develop water soluble chiral ligands has considerable significance, as it enables their metal complexes to catalyse asymmetric transfer hydrogenation in water. Williams *et al*. have reported water soluble analogues **240**-**243**, which are similar to successful chiral ligands TsDPEN **64** and TsCYDN **148**, with an additional sulphonic acid group (Figure 40).[229-230]

These water-soluble ligands **240**-**243** were used for asymmetric transfer hydrogenation of aromatic ketones with $[Ru(p\text{-cymene})Cl_2]_2$ using IPA as the hydrogen source. Compound **240** with a sulfonic acid group on the *para* position, gave 96% conversion with an enantioselectivity of 94% ee for reduction of acetophenone with $[Ru(p\text{-cymene})Cl_2]_2$ (Table 19).[229] Similar substitution in TsCYDN, compound **241** gave a good conversion for acetophenone reduction but only 88% ee with $[Ru(p\text{-cymene})Cl_2]_2$. Compound **242** with a sulfonic group at the *ortho* position, showed total loss in activity with only 11% conversion over period of

48 h for transfer hydrogenation of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ (Table 19).[229]

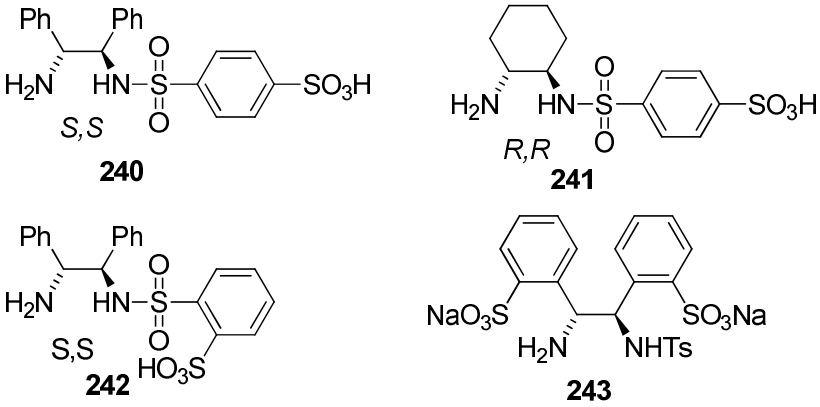


Figure 40: Water soluble chiral ligands.

Table 19: Asymmetric transfer hydrogenation of acetophenone **112** using water soluble chiral ligands **240**-**243** with [Ru(*p*-cymene)Cl_2]$_2$.

Ligands	Hydrogen source	S/C	Solvent	Temp	Time	% Yield	% ee
240	IPA/KO^{t}Bu	100	H_2O	22 ^oC	48h	96	94(*S*)
241	IPA/KO^{t}Bu	100	H_2O	22 ^oC	48 h	91	88(*R*)
242	IPA/KO^{t}Bu	100	H_2O	22 ^oC	48 h	11	91(*S*)
243	HCOONa	100	H_2O/ PTC	40 ^oC	24 h	>99	95(*R*)

Another water-soluble chiral ligand **243** has been reported by Deng (Figure 40).[230] Compound **243** is found to be highly water soluble due to the presence of two sulfonate groups. It exhibited good activity and excellent enantioselectivity for

asymmetric transfer hydrogenation of ketones with [Ru(*p*-cymene)Cl_2]$_2$ in the presence of the phase transfer catalyst SDS (sodium dodecyl sulphate).[230] Compound **243** gave almost complete conversion and 95% ee for transfer hydrogenation of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ at 40 ^oC in 24 h using sodium formate as the hydrogen source under reaction conditions. Compound **243** has been recycled two times without any loss of enantioselectivity (Table 19).[230]

Asymmetric transfer hydrogenation using chiral-metal complexes is now a well developed field. It has now been used on an industrial scale for the synthesis of biologically active compounds. However, the process is required to be economical, on large scale synthesis. Use of transition metal makes the process quite expensive due to price of chiral ligands and metal. Due to this, it is desirable to make asymmetric transfer hydrogenation a heterogeneous reaction, which will allow the catalyst to be recovered and it can then be recycled. Immobilisation of catalysts can be achieved by preparing solid supported chiral ligands. Xiao *et al*. have reported water-soluble polyethylene glycol-supported TsDPEN (PTsDPEN) **244** (Figure 41).[186,231]

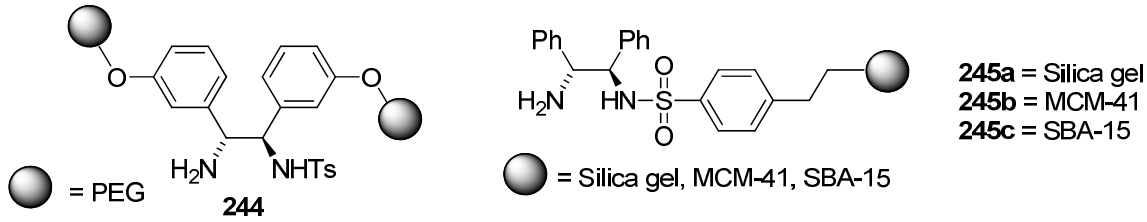
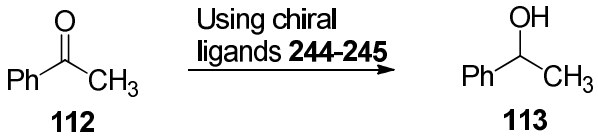


Figure 41: Supported chiral ligands.

For initial investigations, PTsDPEN compound **244** was used for asymmetric transfer hydrogenation of ketones in combination with [Ru(*p*-cymene)Cl_2]$_2$ in FA:TEA. It has shown good activity and enantioselectivity, but to recycle the catalyst use of green solvent is required such as water. Compound **244** gave very

high (99%) conversion and good enantioselectivity (92% ee) for transfer hydrogenation of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ in H_2O with sodium formate as the source of hydrogen at 40 ^oC (Table 20). [186,231] This PTsDPEN catalyst with [Ru(*p*-cymene)Cl_2]$_2$ can be reused in the reduction of acetophenone in water, just by extracting the product with diethyl ether along with addition of fresh acetophenone and 1 equivalent of formic acid. Moreover, there was no deterioration in enantioselectivity after more than 10 cycles. [186,231]



112 **113**

Table 20: Asymmetric transfer hydrogenation of acetophenone **112** using supported chiral ligands **244**-**245** with [Ru(*p*-cymene)Cl_2]$_2$.

Ligands	Hydrogen source	S/C	Solvent	Temp	Time	% Yield	% ee
244	FA:TEA	100		50 ^oC	20 h	95	94(*R*)
244	HCOONa	100	H_2O	40 ^oC	1 h	99	92(*R*)
245a	HCOONa	100	H_2O	40 ^oC	9 h	>99	91(*R*)

Another efficient supported ligand was reported by the Tu group.[232] The silica gel-supported TsDPEN ligand **245** has been found to be a very efficient catalyst in both organic and aqueous solvents for asymmetric transfer hydrogenation of ketones with [Ru(*p*-cymene)Cl_2]$_2$. Supported compounds **245a**-**245c** were used for asymmetric transfer hydrogenation of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ with sodium formate in water (Figure 41, Table 20-21).[232] Compound **245a** was able to reduce acetophenone in 9 h with 91% ee with [Ru(*p*-cymene)Cl_2]$_2$. This result was improved by using the phase transfer catalyst, tetrabutylammonium bromide

(TBAB). Compound **245a** gave a much faster conversion (>99% in 2h) for acetophenone with high enantioselectivity of 96% ee using [Ru(*p*-cymene)Cl_2]$_2$. Moreover, this supported ligand **245a** can be reused up to 6 times for hydrogenation of acetophenone in combination with [Ru(*p*-cymene)Cl_2]$_2$ without loss in enantioselectivity or yields (Table 21). At the same time, a ligand supported with MCM-41 **245b** and SBA-15 **245c**, was found to be recyclable in up to 5 runs, but reactions were much slower compared to **245a** using [Ru(*p*-cymene)Cl_2]$_2$ (Table 21).[232]

Table 21: Recycling supported chiral ligands **245a-c** with [Ru(*p*-cymene)Cl_2]$_2$ for asymmetric transfer hydrogenation of acetophenone **112**.

245a				**245b**				**245c**			
Run	Time	% conv	% ee	Run	Time	% conv	% ee	Run	Time	% conv	% ee
1-3	2 h	>99	96	1-3	5 h	>99	93	1-5	6-28 h	>99-99	94-95
4-6	3.5-12 h	>99-99	96	4-5	6-37 h	87-89	93	6	90 h	92	95
7	60 h	66	96								

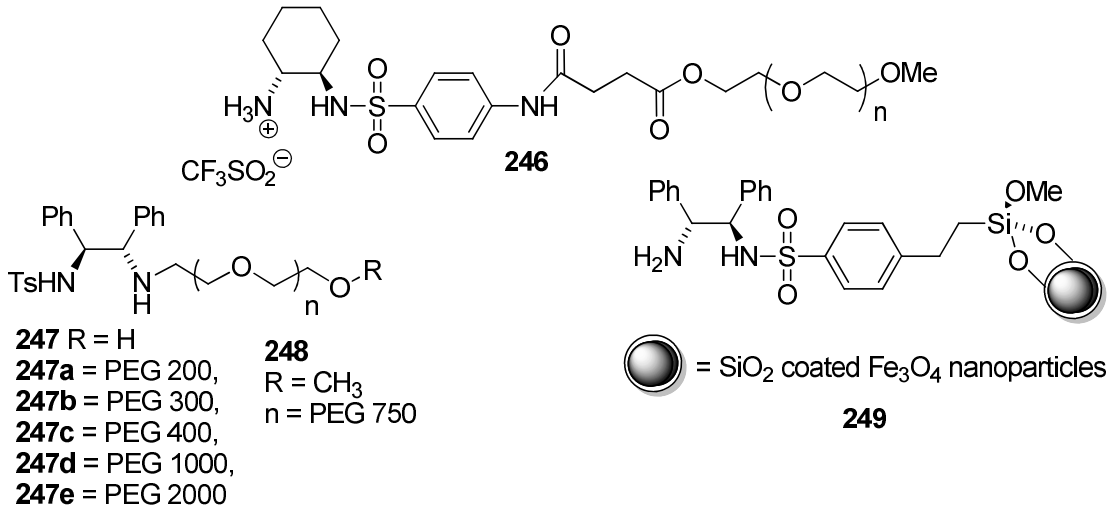
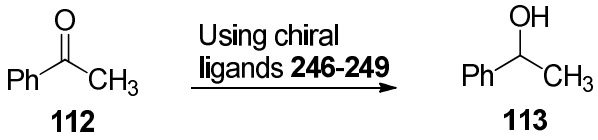


Figure 42: Supported chiral ligands.

Recently, Zhou and Ma have reported PEG supported TsCYDN **246** and used this for asymmetric transfer hydrogenation of ketones with [Ru(*p*-cymene)Cl_2]$_2$ using sodium formate in water (Figure 42).[233] Compound **246** gave complete transfer hydrogenation of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ at 40 ^oC in 6 h with 86.5% ee (Table 22). Moreover, the catalyst can be easily separated from reaction mixture and recycled up to four cycles with no change in enantioselectivity. But fourth reaction cycle was found to be slower (Table 23).[233]



112 **113**

Table 22: Asymmetric transfer hydrogenation of acetophenone **112** using supported chiral ligands **246**-**249** with [Ru(*p*-cymene)Cl_2]$_2$.

Ligands	Hydrogen source	S/C	Solvent	Temp	Time	% Yield	% ee
246	HCOONa	100	H_2O	40 ^oC	6 h	100	86.5(*R*)
247e	HCOONa	100	H_2O	40 ^oC	15 h	>99	94(*S*)
248	HCOONa	100	H_2O	40 ^oC	15 h	>99	94(*S*)
249	HCOONa	100	H_2O	40 ^oC	1 h	97.2	97.7(*R*)

Li *et al*. have reported a series of *N*-pegylated TsDPEN derivatives **247a-e**, **248** as chiral ligands for asymmetric transfer hydrogenation of ketones with [Ru(*p*-cymene)Cl_2]$_2$ using sodium formate in water (Figure 42).[234] All of them have shown high activity with almost complete reduction of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ in 15 h at 40 ^oC and ~ 94% ee (Table 22). Compound **247e** was found to be efficient in up to ten catalytic cycles without any deterioration in enantioselectivity for reduction of acetophenone in combination with [Ru(*p*-

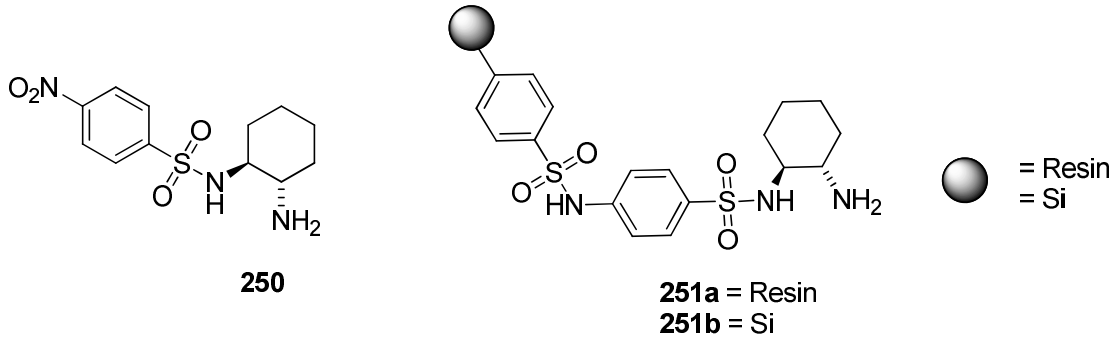
cymene)Cl_2]$_2$ (Table 23). At the same time compound **248** was also found to be good in up to six catalytic cycles with [Ru(*p*-cymene)Cl_2]$_2$ but after that the reaction became much slower with just 1% drop in ee (Table 23).[234]

Table 23: Recycling of supported chiral ligands **246**, **247e** and **248** with [Ru(*p*-cymene)Cl_2]$_2$ for Asymmetric transfer hydrogenation of acetophenone **112** using HCOONa and water.

246				**247e**				**248**			
Run	Time	% conv	% ee	Run	Time	% conv	% ee	Run	Time	% conv	% ee
1	6 h	100	86.5	1-8	6 h	>99	94	1-5	6 h	>99	93.7
2	6 h	100	86.4	9	6 h	97	93.8	6	6 h	98	93
3	6 h	100	86.5	10	6 h	85	94	7	12 h	80	92.5
4	24 h	73.8	86.6								

More recently, Liu and Li have reported a magnetically recovered SiO_2-coated Fe_3O_4 nanoparticles attached to TsDPEN for asymmetric transfer hydrogenation of aromatic ketones with Rh in water.[235] For asymmetric transfer hydrogenation of acetophenone, compound **249** gave 97.2% conversion with high enantioselectivity of 97.7% ee in 1 h reaction time with [RhCp*Cl_2]$_2$ at 40 ^oC using sodium formate and PTC (TBAB) in water (Figure 42, Table 22). Moreover, the catalyst can be recovered by using a small magnet and showed the same catalytic activity in up to ten consecutive reactions with 91.9% conversion and 92.5% ee for reduction of acetophenone.[235] Silica supported TsCYDN ligands **251a-b** has been reported by Somnathan for asymmetric transfer hydrogenation of ketones using RhCp* complex in water (Figure 43).[236] The supported catalyst can be easily synthesised from

compound **250** with reduction of the nitro group to an amine followed by reaction with silica or resin.[236]

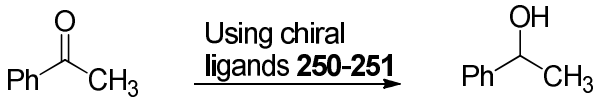


250

251a = Resin
251b = Si

Figure 43: Supported chiral ligands.

First, compound **250** was employed for the reduction of acetophenone with $[RhCp^*Cl_2]_2$ to give almost complete conversion in 0.3 h with 93% ee. Immobilized ligand **251a** gave a good conversion (98%) and good enantioselectivity (84% ee), but a deterioration in enantioselectivity was observed during reuse with $[RhCp^*Cl_2]_2$ (Table 24). On other hand, compound **251b** also gave a good conversion for reduction of acetophenone with $[RhCp^*Cl_2]_2$, but with very low (46% ee) enantioselectivity (Table 24).[236]



112 **113**

Table 24: Asymmetric transfer hydrogenation of acetophenone **112** using supported chiral ligands **250-251** with $[RhCp^*Cl_2]_2$.

Ligands	Hydrogen source	S/C	Temp	Time	% conv	% ee
250	$HCOONa/H_2O$	300	40 ^oC	0.3 h	>99	93
251a	$HCOONa/H_2O$	100	40 ^oC	-[a]	98	84
251b	$HCOONa/H_2O$	100	40 ^oC	-[a]	93	46

[a] The reaction was monitored by TLC for complete conversion.

Zhou *et al*. have reported chiral TsDPEN derivatives **252-253** with an imidazolium group as the chiral ligand for asymmetric transfer hydrogenation with Ru using FA:TEA in an ionic liquid [bmim][PF_6] (Figure 44).[237] Chiral ligand **252** gave complete reduction of acetophenone with 97% ee at 40 ^oC in 8 h using [Ru(*p*-cymene)Cl_2]$_2$. Unfortunately, during recycling of the catalysts, the reaction became slower and slower for reduction of acetophenone, although without any major drop in enantioselectivity. Compound **253** also showed similar activity for reduction of acetophenone with [Ru(*p*-cymene)Cl_2]$_2$ but low enantioselectivity (84% ee) (Table 25).[237]

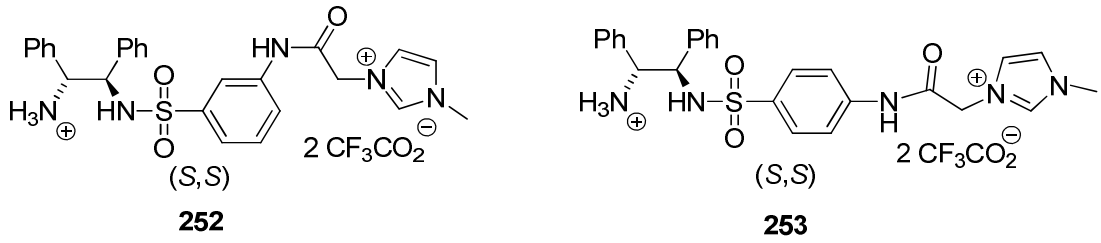


Figure 44: Chiral ligands with imidazolium group.

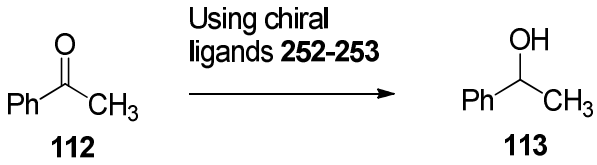


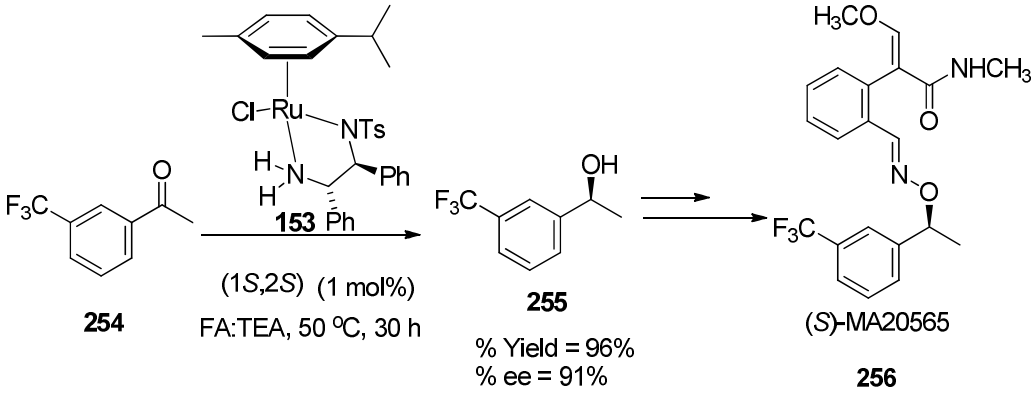
Table 25: Asymmetric transfer hydrogenation of acetophenone **112** using supported chiral ligands **252-253** with [Ru(*p*-cymene)Cl_2]$_2$.

Ligands	Run	Hydrogen source	S/C	Solvent	Temp	Time	% conv	% ee
252	1	FA:TEA	100	[bmim][PF_6]	40 ^oC	8 h	100	97(*R*)
	2					22 h	100	96(*R*)
	3					80 h	100	94(*R*)
253		FA:TEA	100	[bmim][PF_6]	40 ^oC	8 h	100	86(*R*)

1.4.9 Application to pharmaceutical targets

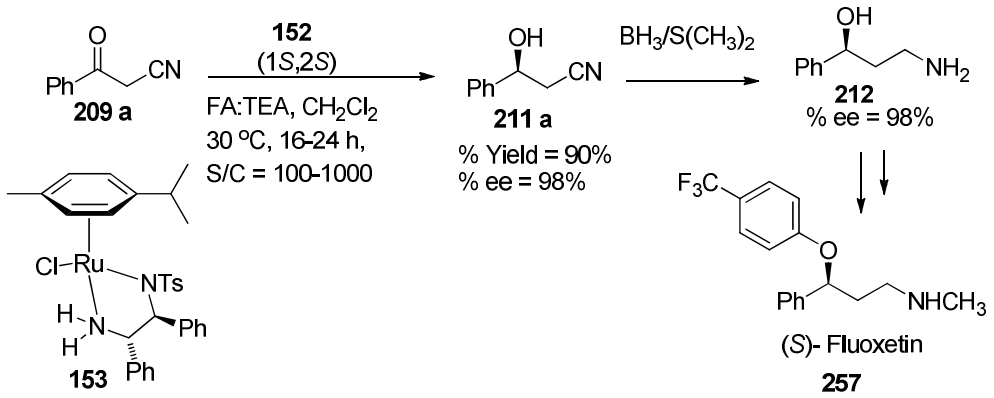
1.4.9.1 Synthetic studies towards MA-20565

Substituted acetophenone was reduced with high enantioselectivity using compound **153**. Tanka *et al*. have reported the asymmetric transfer hydrogenation of 3-trifluoromethylcetophenone **254** using compound **153** to the corresponding (*S*)-alcohol **255** with 96% yield and 91% ee (Scheme 32).[238] This (*S*)-3-trifluoromethylphenyl ethanol **255** is a key intermediate for the synthesis of MA-20565 **256**, a wide-spectrum agricultural fungicide.[238]



Scheme 32: Synthesis towards MA-20565.

1.4.9.2 Synthesis towards *(S)*-Fluoxetine

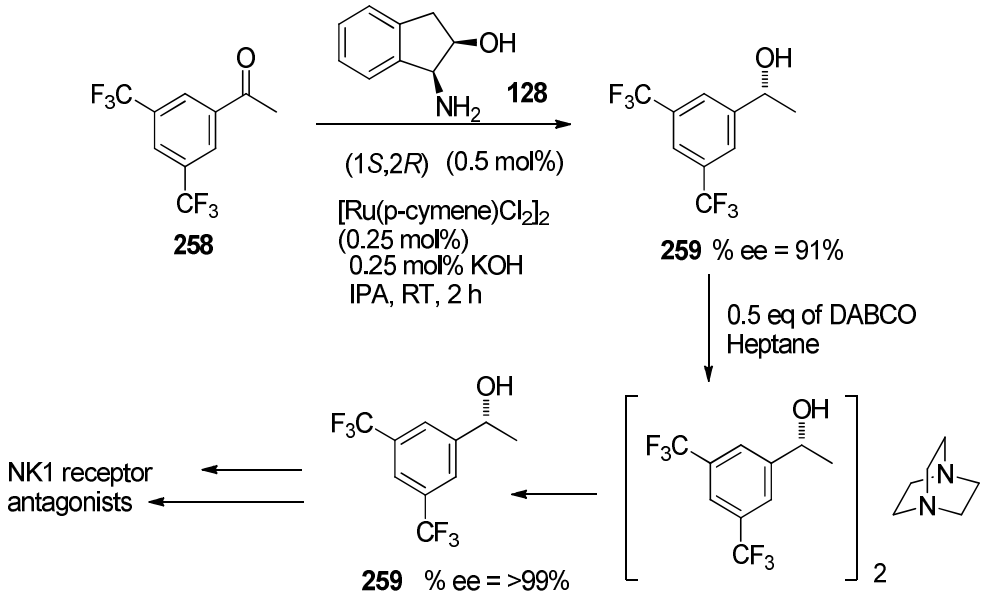


Scheme 33: Synthesis towards *(S)*-Fluoxetine.

Ikariya has reported a practical synthesis of (*S*)-Fluoxetine **257** by using asymmetric transfer hydrogenation.[219] Compound **153** gave enantioselective reduction of 2-cyanoacetophenone **209a** using FA:TEA in 98% ee. The resulting alcohol product **210a** was reduced using $BH_3/S(CH_3)_2$ to give amino alcohol compound **211**, an important intermediate towards the synthesis of (*S*)-Fluoxetine **257** (Scheme 33).[219]

1.4.9.3 An intermediate for NK1 receptor antagonist compounds

Optically pure 3,5-bistrifluoromethylphenyl ethanol is one of the important parts of NK-1 receptor antagonists. 3,5-Bistrifluoromethylphenyl ethanol **259** can be synthesised with good optical purity (~91% ee) using different chiral ligands and Ru/Rh complexes.[239] On an industrial scale, commercially available (1*S*,2*R*)-*cis*-aminoindanol **128** has been used with $[Ru(p\text{-cymene})Cl_2]_2$ in IPA/KOH to give high conversion (98%) and good enantioselectivity of 91% ee for reduction of compound **258** (Scheme 34). Interestingly, by using a modified method the optical purity of **259** can be improved to >99%; this requires cocrystallization of compound **259** with DABCO (Scheme 34). [239]



Scheme 34: An intermediate for NK1 receptor antagonist compounds.

1.5 Summary

In asymmetric catalysis, organometallic catalysis is a well developed area and organocatalysis has also given promising results. Small molecules derived from enantiomerically pure natural products such as amino acids and alkaloids have shown good activity for C-C, C-N and C-X bond formation reactions. Recently, enantiomerically pure diamine ligands have also been found to be good as asymmetric organocatalysts and L-proline in particular works well for a range of asymmetric reactions. A range of novel chiral diamine derivatives can be employed as asymmetric organocatalysts.

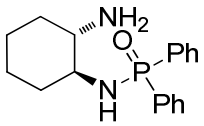
Chiral ligands and metal complexes developed for asymmetric transfer hydrogenation of ketones and imines have been discussed. Mechanistic studies carried out by various research groups suggest that there are different mechanisms for asymmetric transfer hydrogenation of ketones and imines. Substituted chiral complexes can be used to get more insight into this mechanistic difference between ketone and imine reductions.

Asymmetric transfer hydrogenation using η^6-arene-Ru- complexes was found to be highly efficient and selective for a range of substrates such as aryl alkyl ketones, heterocyclic ketones and imines. The enantioselectivity of products such as alcohols and amines is mostly due to chirality at the metal centre and a CH-π interaction between η^6-arene-Ru and the aryl group of the substrate. Because of this substrates without aryl groups are reduced with lower enantioselectivities. To understand these enantioselectivities, a range of substrates need to be studied in asymmetric transfer hydrogenation using η^6-arene-Ru- complexes.

1.6 Aims and Objectives

Aim: Synthesis of novel chiral diamine ligands, ruthenium metal complexes and investigation of their use as asymmetric catalysts.

Objectives: A series of chiral diamine ligands will be synthesised and employed as asymmetric organocatalysts. The synthesized ligands will be studied for optimization of reaction conditions and stereoselectivity for different asymmetric reactions such as Michael addition, aldol condensation, Diels-Alder reaction, nucelophilic addition, nucleophilic substitution.



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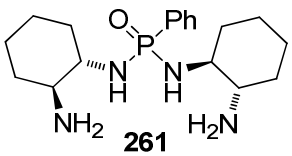

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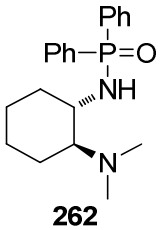

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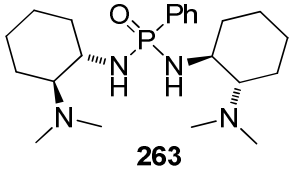
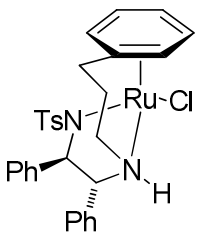


263

Novel ruthenium metal complexes with *N*,*N*-dialkylated chiral ligands will be synthesised to study the asymmetric transfer hydrogenation of ketones and imines to understand the mechanism of reduction for both class of substrates. Ketones with hindered group at the α-position will be synthesized and used for asymmetric transfer hydrogenation using Ru-3C-tethered catalyst **181**, which will give more insight into the substrate scope of this transformation.



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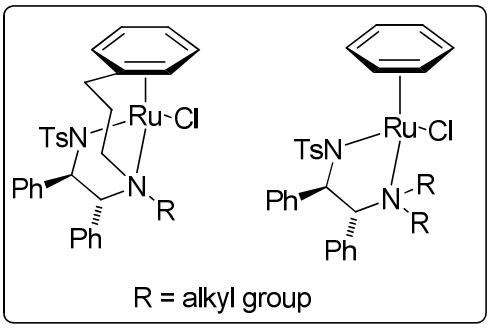
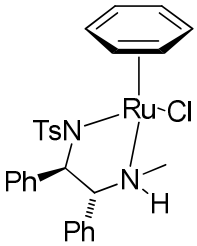




193a

2 Results and Discussion

2.1 Synthesis and applications of derivatives of 1,2-cyclohexanediamine as asymmetric organocatalyst

As discussed in section 1.3.2, derivatives of 1,2-cyclohexanediamine and 1,2-diphenyl-1,2-ethanediamine have been used as organocatalysts for asymmetric reactions. During the investigation into the use of new ligands for asymmetric transfer hydrogenation carried out by the Wills group, (1*R*,2*R*)-PODPEN **56** was studied as an asymmetric organocatalyst for the Michael addition of ketones to *trans*-β-nitrostyrene as discussed in section 1.3.2.1.[76] For initial investigations, similar derivatives of 1,2-cyclohexanediamine **260-264** (Figure 45) were selected to synthesise and study as asymmetric organocatalysts.

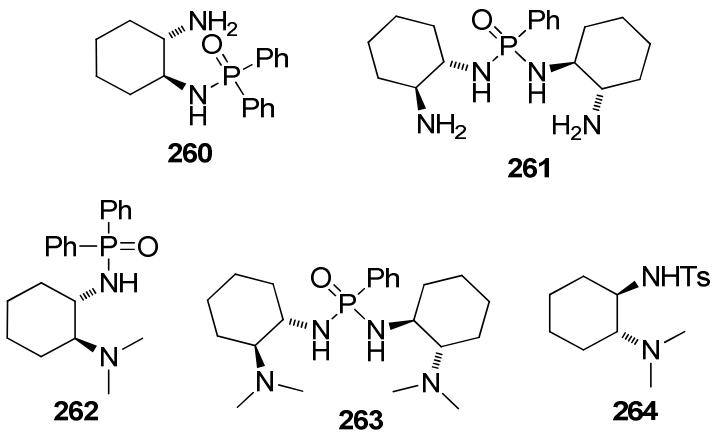
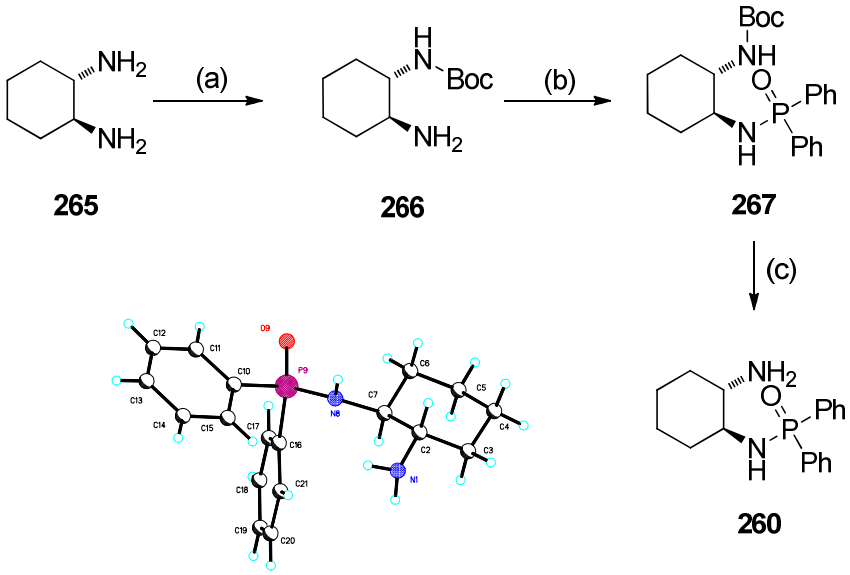


Figure 45: Derivatives of 1,2-cyclohexanediamine.

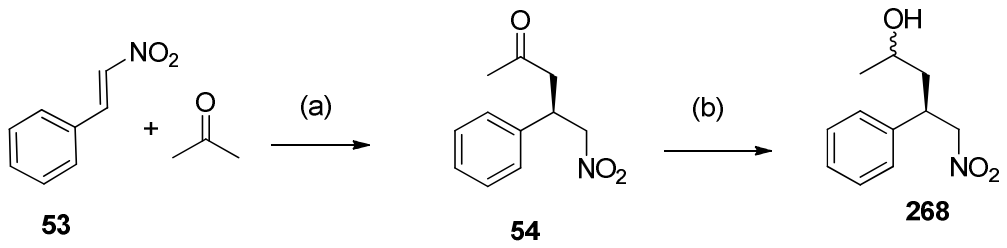
Compound **260** was synthesised as outlined in Scheme 35 starting from the mono Boc- protection of 1,2-cyclohexanediamine **265** followed by reaction with diphenylphosphinic chloride to afford compound **267**. Deprotection of the Boc-group of **267** using TFA resulted in the formation of compound **260**.



Reagents and Conditions: (a) $(Boc)_2O$, DCM, 20-21 °C, 18 h, 81%; (b) Ph_2POCl, NEt_3, DCM, 0 °C, 2 h, 94%; (c) CF_3COOH, DCM, 20 °C, 1.5 h, NEt_3, 0 °C, 68%.

Scheme 35: Synthesis of (1*S*,2*S*)-*N*-(diphenylphosphinyl)-1,2-diaminocyclohexane.

The Michael addition of acetone to *trans*-β-nitrostyrene **53** (Scheme 36) was attempted with compound **260** taking toluene as the solvent. The reaction was monitored by ^{1}H-NMR at different time intervals. There was no increase in the conversion above 27% from 72 h to 5 days (Table 26, Entry 1) by ^{1}H-NMR. The reaction solvent was changed to hexane and this was found to be better, giving an increase in conversion to 57% after 27 h. Again no further increase was seen in conversion after 5 days by ^{1}H-NMR. The reaction was worked up at this stage and the product was isolated in 79% ee (major enantiomer *R*) (Table 26, Entry 2). In order to calculate the enantiomeric excess, compound **54** was reduced to its alcohol derivative **268** using $NaBH_4$ and the stable product was analysed by chiral HPLC. These results suggest that catalytic activity of compound **260** may be inhibited during the reaction; hence the reaction did not proceed to complete conversion

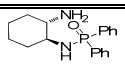
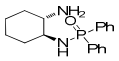


53 **54** **268**

Reagents and Conditions: (a) Catalyst (10 mol%), acetic acid, water, solvent, 20-21 °C, 5 days; (b) $NaBH_4$, MeOH, 20-21 °C, 1 h

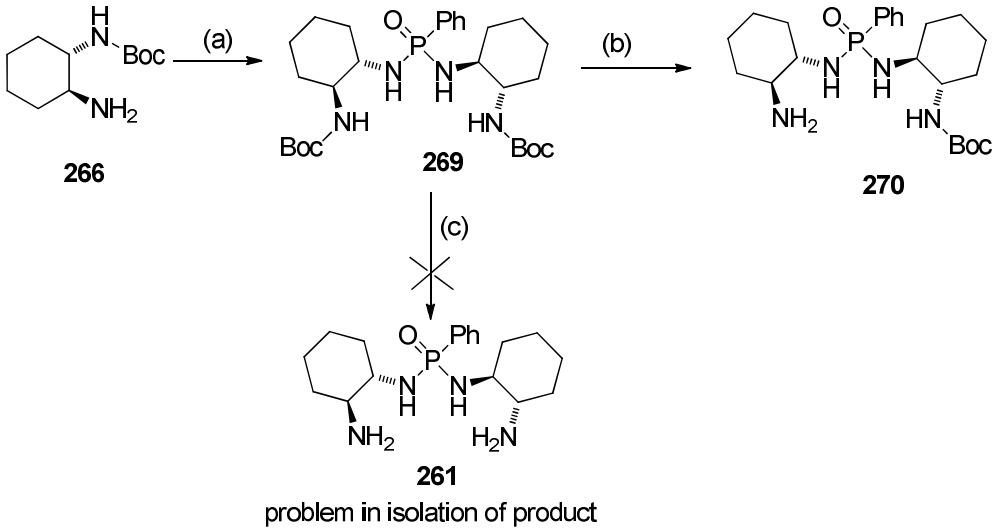
Scheme 36: Michael addition of acetone to *trans*-β-nitrostyrene using compound **260.**

Table 26: Michael addition of acetone to *trans*-β-nitrostyrene using compound **260.**

Entry	Catalyst	Solvent	Time	%Conv[a]	%ee[b]
1	 **260**	Toluene	72 h 5 days	27% 27%	ND
2	 **260**	Hexane	27 h 72 h 5days	57% 57% 57%	79% (*R*)

[a] The % conversion are calculated on basis of ^{1}H-NMR. [b] The enantiomeric excess is calculated from chiral HPLC data for reduced product, major enantiomer *R*. ND Not determined.

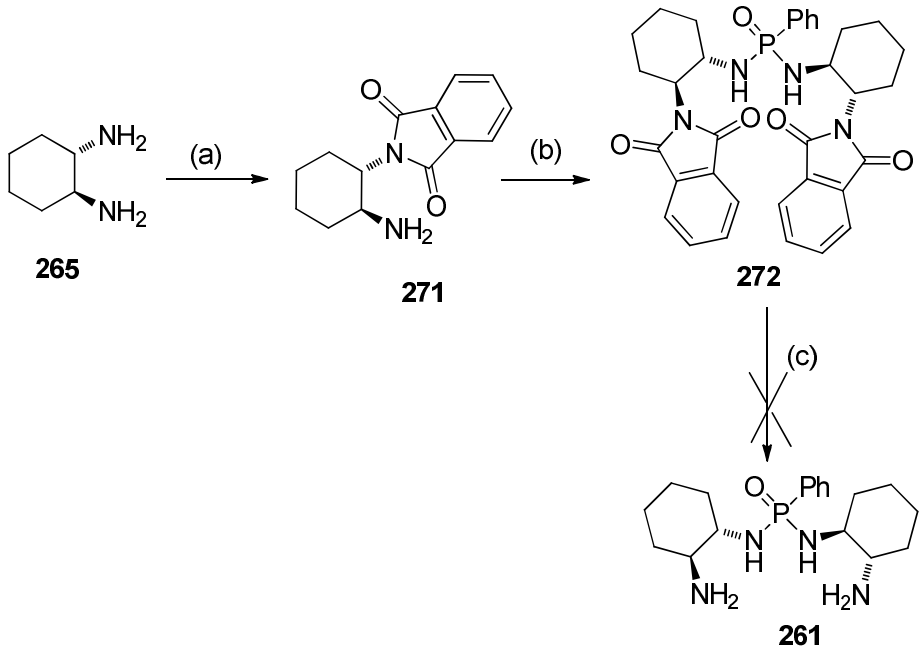
The bifunctional catalysts containing urea and thiourea groups have shown superior catalytic activity for Michael addition reactions as discussed in section 1.3.2.1. Compound **261** was selected for synthesis as having two 1,2-cyclohexanediamine rings attached to the P(O)Ph group may give similar activity to bifunctional catalysts. To synthesise compound **261**, compound **266** was reacted with phenylphosphonic dichloride to give compound **269**. The Boc- deprotection of **269** using TFA was unsuccessful due to the decomposition of the product during the work up. The Boc- deprotection of **269** was attempted with zinc dibromide, however this resulted in the mono deprotection to compound **270** in poor yield (Scheme 37).



Reagents and Conditions: (a) Ph_2POCl, DIPEA, DCM, -5- 22 ^oC, 3.5 h, 47%; (b) $ZnBr_2$, dry DCM, 19-20 ^oC, 24 h, 24%; (c) CF_3COOH, DCM, 20 ^oC, 1h, 0 ^oC, NEt_3, 0%.

Scheme 37: Attempted synthesis of (1*S*,2*S*)-phenylphosphonic bis(1-amino-2-cyclohexylamide) **261**.

In view of the problems encountered during the removal of the Boc- group and the low stability of the product under acidic conditions, the use of a phthalimide protecting group was investigated as described in Scheme 38. Compound **261** was synthesised by mono protection of 1,2-cyclohexanediamine **265**. The mono protected compound **271** was reacted with phenylphosphonic dichloride to afford compound **272**, however the deprotection of compound **272** using hydrazine hydrate resulted in the formation of a product with low molecular weight with [M+H]+ = 283.0 peak in ESI-MS instead of the required product **261**.



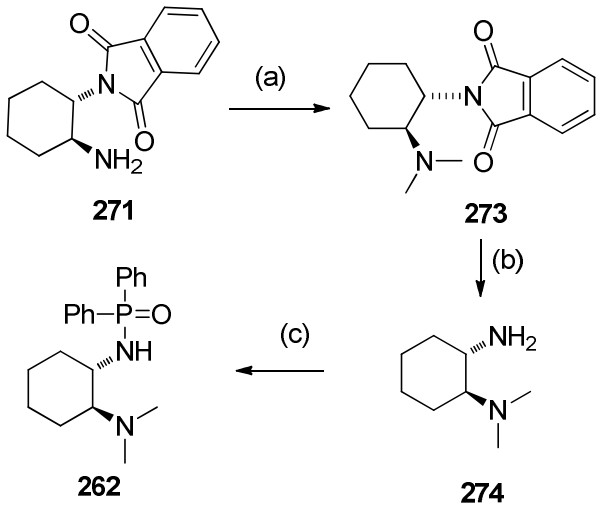
265 271 272 261

Reagents and Conditions:(a) Phthalic anhydride, p-TsOH, p-Xylene, 130 ^{o}C, 1 h; 100 ^{o}C, solid separation, 91%; (b) Ph_2POCl, DIPEA, DCM, -5- 22 ^{o}C,18 h, 48%.; (c) NH_2NH_2. H_2O, EtOH, 78 ^{o}C, 2 h.

Scheme 38: Attempted synthesis of (1*S*,2*S*)-phenylphosphonic bis(1-amino-2-cyclohexylamide) **261**.

During the attempts made to synthesis compound **261**, the deprotection step resulted in decomposition of the product under both acidic and basic conditions. This may be due to the presence of the basic amino group or instability of the -$(NH)_2$P=O group. To overcome this problem with the deprotection step during synthesis, the compound containing a dimethylamino group instead of a free amine was selected for the synthesis.

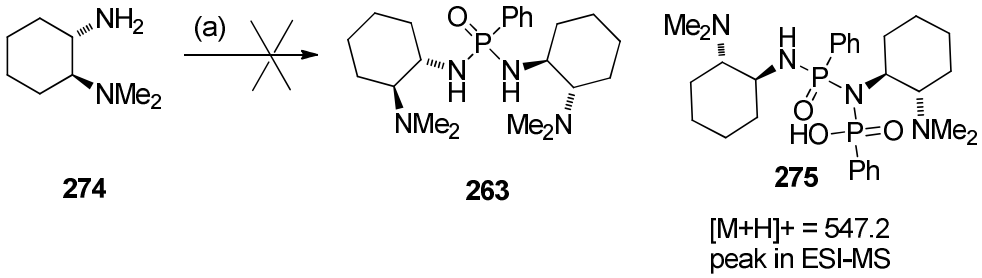
Compound **262** was synthesised by the route outlined in the Scheme 39 starting from the mono phthalimide protected compound **271** followed by dimethylation to give **273**. Compound **273** was deprotected using hydrazine to give amine derivative **274**, which was further reacted with diphenylphosphinic chloride to give compound **262**.



Reagents and Conditions: (a) HCHO (37 % aq.), HCOOH, 78 °C, 6 h, 56%; (b) NH_2NH_2. H_2O, EtOH,78 °C, 2 h, 63%; (c)Ph_2POCl, DIPEA, DCM, -30- 22 °C, 2 h, 47%.

Scheme 39: Synthesis of (1*S*,2*S*)-*N*,*N*-dimethyl-*N'*-(diphenylphosphinyl)-1,2-diaminocyclohexane **262**.

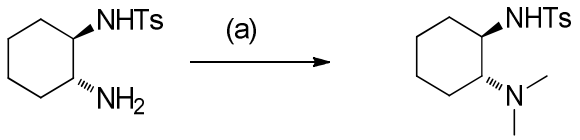
In contrast, the reaction of **274** with phenylphosphonic dichloride resulted in the formation of compound **275** instead of the required product **263** (Scheme 40). The ^{31}P-NMR spectrum of compound **275** exhibited two phosphorus peaks and HRMS showed a high molecular weight, whilst the ^{1}H-NMR was quite complex. On the basis of the data obtained, compound **275** may be assigned the structure shown in the Scheme 40.



Reagents and Conditions: (a) $PhPOCl_2$, DIPEA, DCM, -5- 22 °C, 2 h.

Scheme 40: Attempted synthesis of (1*S*,2*S*)-phenylphosphonic bis(*N*,*N*-dimethyl-cyclohexyl-2-amide) **263**.

Compound **264** was selected to compare the tosyl group with the $Ph_2P(O)$group of compound **262**. Compound **264** was synthesised from the tosyl derivatives **148** by dimethylation as outlined in Scheme 41.

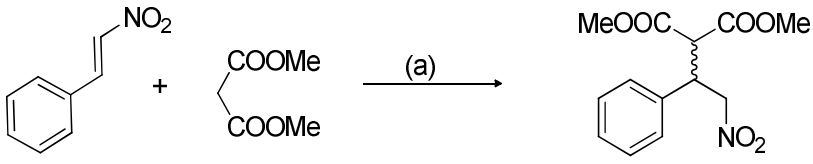


148 **264**

Reagents and Conditions: (a) HCHO (37 % aq.), HCOOH, 78 ^{o}C, 6 h, 81%.

Scheme 41: Synthesis of (1*R*,2*R*)-*N*,*N*-Dimethyl-*N*'-tosyl-1,2-diaminocyclohexane **264**.

Compounds **260**, **262** and **264** were selected as catalysts for the Michael addition of 1,3-dicarbonyl derivatives to *trans*-β-nitrostyrene (Scheme 42). The reaction conversion was determined by monitoring with ^{1}H-NMR at different time intervals. The reactions gave very low conversions for the addition reaction with all three compounds **260**, **262** and **264** (Table 27, Entries 1-3). Due to the low conversions, the enantiomeric excess was not determined for these reactions.

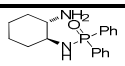
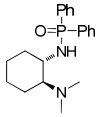


53 **72**

Reagents and Conditions: (a) Catalyst (10 mol%), Toluene, 20-21 ^{o}C, 41 h - 7 days

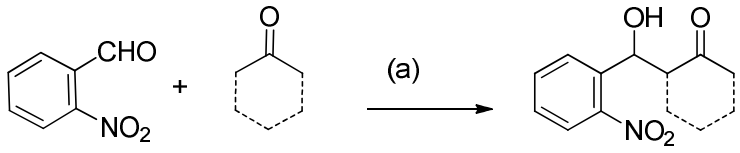
Scheme 42: Michael addition of dimethyl malonate to *trans*-β-nitrostyrene using compounds **260**, **262** and **264**.

Table 27: Michael addition of dimethyl malonate to *trans*-β-nitrostyrene using compounds **260**, **262** and **264**.

Entry	Catalyst	Time	%Conv[a]	%ee[b]
1	 **260**	72h	27%	ND
2	 **262**	41h	16%	ND
3	 **264**	7 days	15%	ND

[a] The % conversion are calculated on basis of ^{1}H-NMR. [b] ND Not determined.

The Aldol reactions of aromatic aldehydes with appropriate ketones were attempted under different conditions using compounds **260**, **262** and **264**; however none showed any catalytic activity. Different metal salts were carried out with these compounds to examine their combined effect on the aldol reaction. As shown in Scheme 47, the reactions were tried using a combination of compounds **260**, **262** and **264** with various metal salts. The reactions were monitored by TLC and ^{1}H-NMR for 2-4 days. The reaction mixtures were purified and analysed by chiral HPLC after significant conversion, but none of the reactions were found to be selective for the aldol reaction (Table 28). This showed that there is little or no interaction between compounds **260**, **262** and **264** and the metal salts used for this aldol reaction.

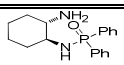
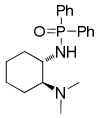


79 **80/92**

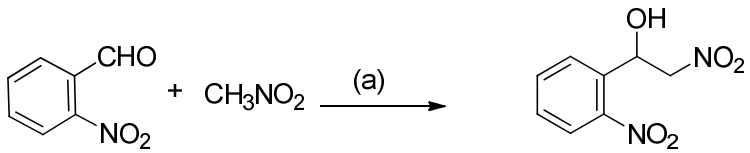
Reagents and Conditions: (a) Catalyst (10 mol%), 19-20 °C, 20 h - 5 days.

Scheme 43: Aldol reaction using compounds **260**, **262** and **264**.

Table 28: Aldol reaction using different compounds **260**, **262** and **264** and the metal complexes.

Entry	Catalyst	Ketone	Metal salt	Time	%Conv[a]	%ee[b]
1	 **260**	Acetone		5 days	NC	
2	 **262**	Acetone	$Zn(OTf)_2$	20h	95%	0%
		Cyclohexanone	$Zn(OTf)_2$	5 days	NC	
		Acetone	$Sc(OTf)_2$	5 days	95%	0%
3	 **264**	Acetone	$Zn(OTf)_2$	5 days	NC	
		Cyclohexanone	$Zn(OTf)_2$	5 days	NC	
		Acetone	$Sc(OTf)_2$	5 days	90%	0%

[a] The % conversion are calculated on basis of ^{1}H-NMR. [b] The enantiomeric excess is calculated from chiral HPLC data. NC No Conversion on basis of ^{1}H-NMR.

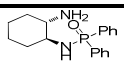
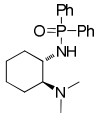


79 **98**

Reagents and Conditions: (a) Catalyst (10 mol%), EtOH, 19-20 °C, 21 h - 4 days

Scheme 44: Henry reaction using compounds **260**, **262** and **264**.

Table 29: Henry reaction of aromatic aldehyde with nitromethane using compounds **260**, **262**, **264** and the metal complexes.

Entry	Catalyst	Metal salt	Time	%Conv.	%ee[a]
1	 **260**	None	22h	100%	0%
		$Cu(OAc)_2$	27h	100%	0%
2	 **262**	CuCl	4 days	100%	2.5%
3	 **264**	CuCl	4 days	100%	27%
		$Cu(OAc)_2$	27h	50%	6%
		$Cu(OTf)_2$	4days	87%	12%
		$Zn(OTf)_2$	21h	100%	0%
		$Sc(OTf)_2$	29h	90%	0%

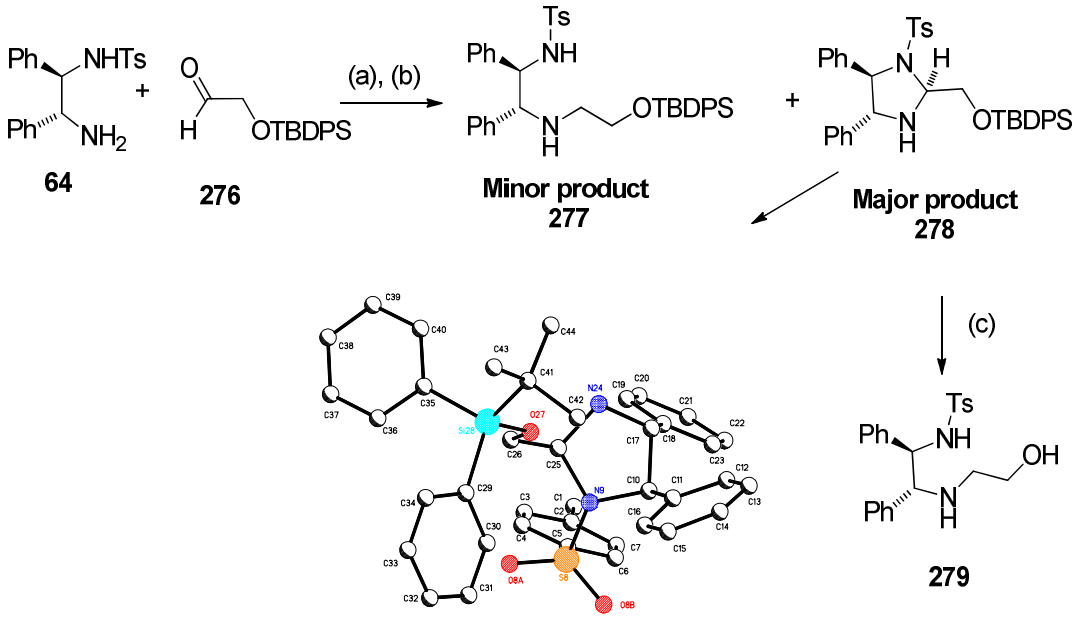
[a] The enantiomeric excess is calculated from chiral HPLC data, major enantiomer *R* .

The Henry reaction was carried out using compounds **260**, **262** and **264** with different metal salts **(**Scheme 44**).** For the Henry reaction, the conversion was quite good using compound **260** and $Cu(OAc)_2$, however no selectivity was observed. The reaction using compound **264** with CuCl showed some interaction between the ligand and metal. However, the reaction was very slow (100% conversion in 4 days) and exhibited low selectivity (27% ee) (Table 29, Entry 3).

Compounds **260**, **262** and **264** were used as asymmetric organocatalysts for different reactions such as the Michael addition, aldol and Henry reactions; however none of the compounds showed good efficiency or selectivity. Derivatives of 1,2-diphenylethanediamine were selected to investigate as asymmetric organocatalysts for different asymmetric reactions.

2.2 Synthesis and application of derivatives of 1,2-diphenylethanediamine as asymmetric organocatalysts

In the literature, a number of ligands for asymmetric transfer hydrogenation catalysts contain 1,2-diphenylethanediamine as a back-bone as discussed in sections 1.4.3 and 1.4.6. In the Wills group, ligands with 1,2-diphenylethanediamine and *N*-tosyl-1,2-diphenylethanediamine have been developed for asymmetric transfer hydrogenation as discussed in section 1.4.6.



Reagents and Conditions: (a) dry MeOH,MS 4Å, AcOH, 20 °C, 4 h; (b) $NaBH_3CN$, 20 °C, 3 h, 96%; (c) $LiAlH_4$, THF, 20 °C, 2 h, 47%.

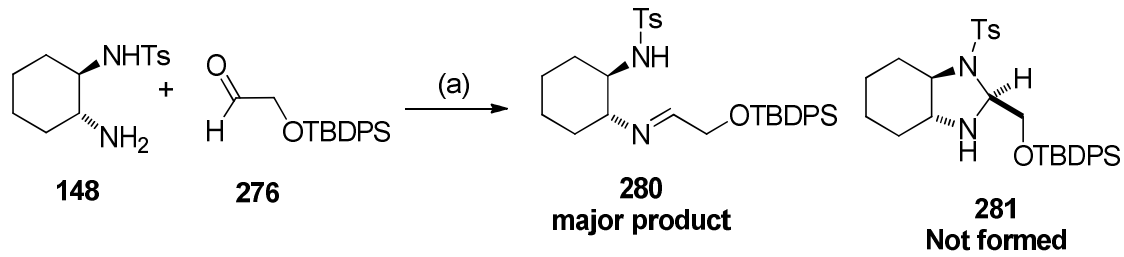
Scheme 45: Isolation of stable cyclic aminal derivative **249.**

During the course of studies on the functionalisation of TsDPEN **64** *via* reductive alkylation,[195,208] its reaction with α-trialkylsilyloxy-substituted aldehyde **276** resulted in the formation of a stable aminal **278** instead of the required compound **277** (Scheme 45). This was not reduced *in situ* under conditions which have typically been previously used for reductive alkylation, e.g. $NaBH_3CN$, MeOH.[206,208] Aminal

278 could be reduced to the required product **279** (the TBDPS group was also removed in this process) using $LiAlH_4$. It was found to be quite stable and could be readily purified by flash chromatography without hydrolysis.

Interestingly, compound **278** was formed significantly as a single diastereoisomer in high yield upon acid-catalysed reaction of **64** with **276** (Scheme 45). The X-ray crystallographic analysis of a purified sample of **278** revealed the relative stereochemistry and the TBDPS group was found to be *trans* to the phenyl adjacent to the basic amine (Scheme 45).

A similar reaction with TsCYDN, compound **148** resulted in the formation of imine **280** instead of cyclic aminal **281**. This may possibly be due to a high level of strain in the bicyclic product **281** (Scheme 46).

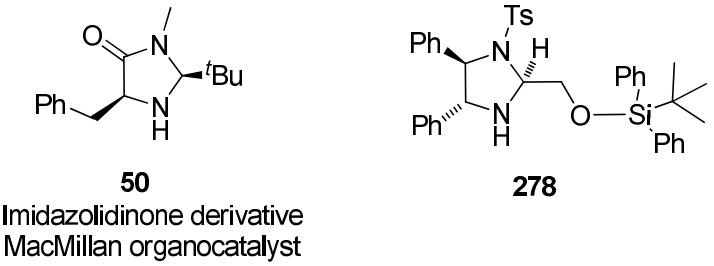


148 **276** **280** **major product** **281** **Not formed**

Reagents and Conditions: dry MeOH,MS 4Å, AcOH, 20 °C, 4 h, 57%.

Scheme 46: Attempted synthesis of cyclic aminal **251.**

The structure of compound **278** can be easily compared with the well known MacMillan organocatalysts **50** (Imdiazolidinone catalysts) (Figure 46). MacMillan organocatalysts have been used as asymmetric organocatalysts for different asymmetric reactions such as the Diels-Alder reaction, the aldol reaction, and the α-functionalization of carbonyl compounds as discussed in sections 1.3.1, 1.3.2.4 and 1.3.2.5 of this thesis.[51-59]



50
Imidazolidinone derivative
MacMillan organocatalyst

278

Figure 46: Structural similarities between MacMillan organocatalyst and compound **278**.

Due to the close structural similarity of compound **278** with **50**, other derivatives **282**-**285** were selected for synthesis and to study as asymmetric organocatalysts (Figure 47).

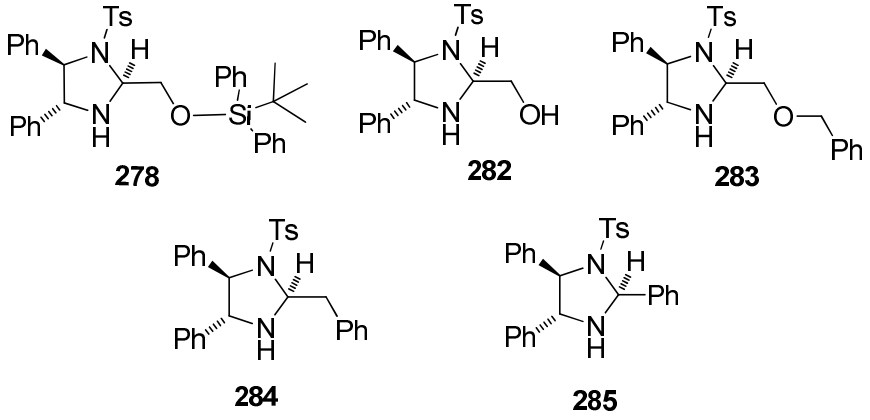
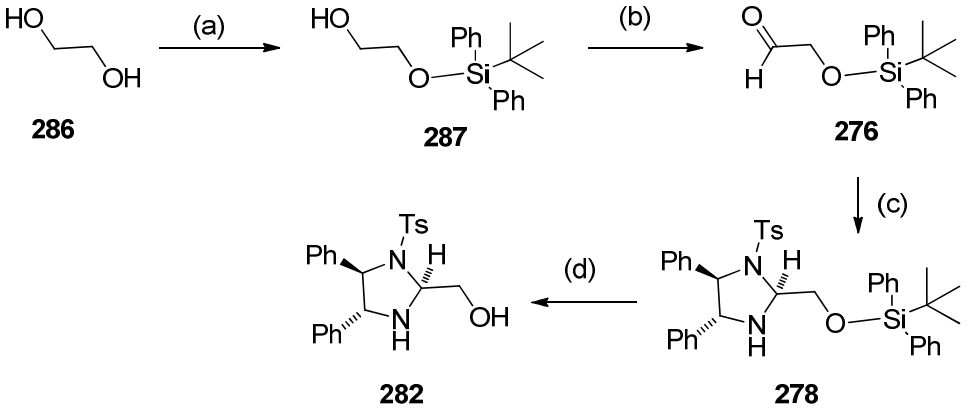


Figure 47: Derivatives of 1,2-diphenylethanediamine **278** and **282**-**285**.

2.2.1 Synthesis of derivatives of 1,2-diphenylethanediamine

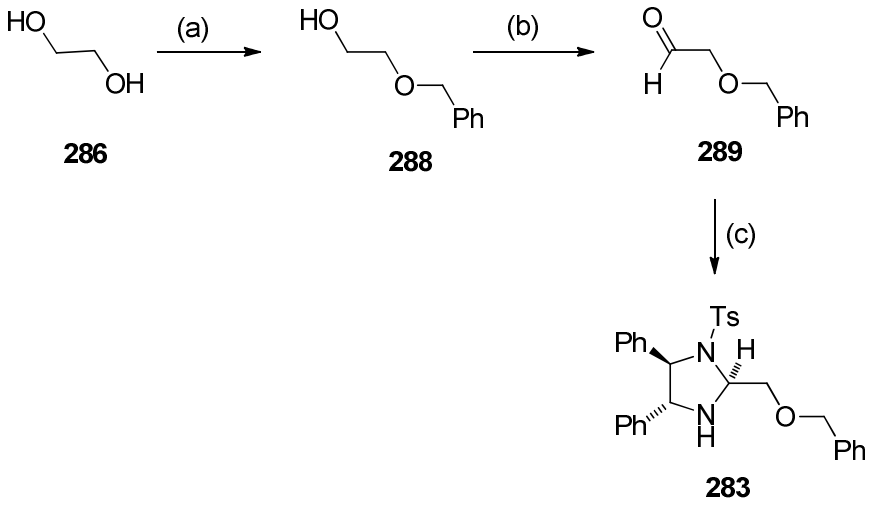
Compound **278** was synthesised following the route outlined in Scheme 47, starting from mono TBDPS- protection of ethylene glycol **286** to give **287** followed by Swern oxidation to give aldehyde **276**. On reaction of aldehyde **276** with TsDPEN in methanol, compound **278** separated out as a white solid. Compound **278** was isolated as a single diastereoisomer by ^{1}H-NMR. The deprotection of compound **278** was carried out using TBAF to give hydroxy derivative **282**.



286 **287** **276** **282** **278**

Reagents and Conditions: (a) Imidazole, dry THF, 20-21 °C, 24 h, 87%; (b) $(COCl)_2$, DMSO, DCM, -78 °C, TEA, -78 to 20 °C, 76%; (c) (1*R*,2R) Ts-DPEN, dry MeOH, MS 4Å, AcOH, 20 °C, 4 h, 80%; (d) TBAF, THF, 20 °C, 24 h, 85%.

Scheme 47: Synthesis of (4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine and (4*R*,5*R*)-4,5-diphenyl-1-tosylimidazolidine-2-methanol.

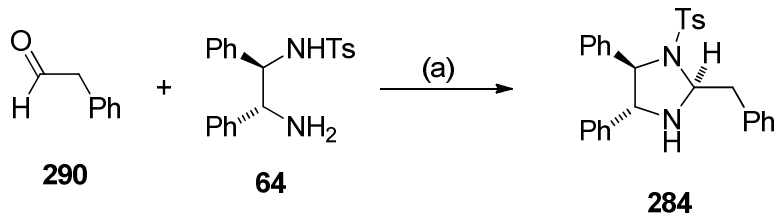


286 **288** **289** **283**

Reagents and Conditions: (a) NaH, DMF, MeOH, 20 °C, 17 h, $C_6H_5CH_2Br$, 20 °C, 24 h, 28%; (b) $(COCl)_2$, DMSO, DCM, -78 °C, TEA, -78 to 20 °C, 76%; (c) (1*R*,2R) Ts-DPEN, dry MeOH, MS 4Å, AcOH, 20 °C, 4 h, 73%.

Scheme 48: Synthesis of (4*R*,5*R*)-2-[(benzyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **283**.

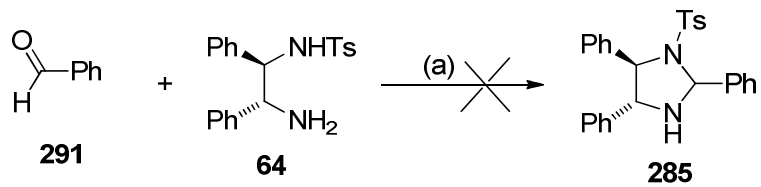
Similarly, compound **283** was synthesised as outlined in Scheme 48, wherein a different protecting group was used. Aldehyde **289** was synthesised by the mono benzylation of ethylene glycol **286** to form compound **288** followed by Swern oxidation. When aldehyde **289** was reacted with TsDPEN no solid precipitated out. The reaction mixture was purified by column chromatography to isolate compound **283** as a single diastereoisomer (relative configuration assigned by analogy with compound **278**). Compound **284** was synthesised by reaction of phenyl acetaldehyde **290** with TsDPEN as outlined in Scheme 49. Compound **284** was found to be less stable during purification compared to compounds **278** and **283**.



Reagents and Conditions: (a) dry MeOH, MS 4Å, AcOH, 20 °C, 4 h, 72%.

Scheme 49: Synthesis of (4*R*,5*R*)-2-benzyl-4,5-diphenyl-1-tosylimidazolidine.

Similarly, the synthesis of compound **285** was attempted by reaction of phenyl acetaldehyde **291** and TsDPEN (Scheme 50). However, both starting materials were recovered during the isolation due to the low stability of compound **285**.

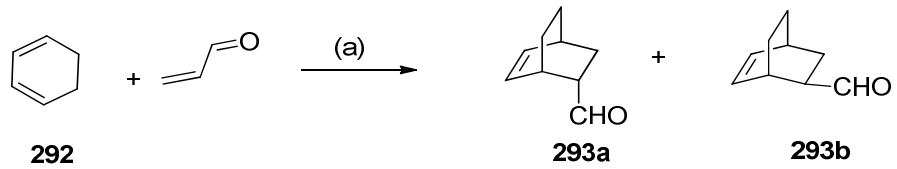


Reagents and Conditions: (a) dry MeOH, MS 4Å, AcOH, 20 °C, 4 h, 72%.

Scheme 50: Attempted synthesis of (4*R*,5*R*)-2-benzyl-4,5-diphenyl-1-tosylimidazolidine.

2.2.2 Application of derivatives of 1,2-diphenylethanediamine as asymmetric organocatalysts

MacMillan organocatalysts are highly efficient and selective for the Diels-Alder reaction as discussed in section 1.3.2.4.[51] Due to the structural similarity of compounds **278**, **282-284** with compound **50**, the Diels-Alder reaction was selected for initial investigation. The Diels-Alder reaction (Scheme 51) between 1,3-cyclohexadiene and acrolein was carried out using TsDPEN and compounds **278** and **282-284**.



292 **293a** **293b**

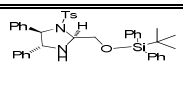
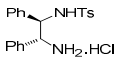
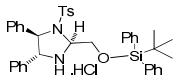
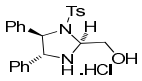
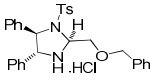
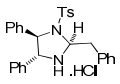
Reagents and Conditions: (a) Catalyst (10 mol%), CH_3CN: H_2O (95:5),19-20 °C

Scheme 51: Diels-Alder reaction using compounds **278**, **282-284**.

For the test reaction between 1,3-cyclohexadiene and acrolein in acetonitrile:water (95:5), compound **278** gave a conversion in 22.5 h, without any selectivity. To cross check the stability of compound **278**, the same reaction was carried out using TsDPEN **64**, however there was no conversion. Since the imidazolidinone catalyst **50** is used as a salt, the reaction was carried out using the hydrochloride salt of TsDPEN **64**. The reaction using the hydrochloride salt of TsDPEN **64** gave complete conversion in 23.5 h with 27% ee and *endo*:*exo* 7:1 (calculated by ^{1}H-NMR) (Table 30, Entry 2). Under the similar set of reaction conditions, the hydrochloride salt of compound **278** gave complete conversion in 24 h and predominantly the *endo* cycloaddition product with an improved enantioselectivity of 72% ee for the *endo* product (Table 30, Entry 3). The cycloaddition reaction using the hydroxyl analogue,

compound **282**.HCl was completed in 18.5 h with exclusive *endo* product with a low enantioselectivity of only 44% ee (Table 30, Entry 4). The benzyloxy analogue compound **283**.HCl also exhibited similar catalytic activity with a product of 45% ee (Table 30, Entry 5).

Table 30: Diels-Alder reaction of 1,3-cyclohexadiene and acrolein using compounds **278**, **282**-**284**.

Entry	Catalyst	Time	Yield[a]	%ee[b]	endo:exo
1	 **278**	22.5h	23.5%	0%	ND
2	 **64**	22.5h	30%	27% (*S*)	7:1
3	 **278**	24h	41%[c]	72% (*S*)	12:1
4	 **282**	18.5h	36%	44% (*S*)	12:1
5	 **283**	17.5h	35%	45% (*S*)	10:1
6	 **284**	17.5h	35%	28% (*S*)	5:1

[a] The % yields are calculated on basis of isolated product, [b] The enantiomeric excess was calculated from chiral GC data, an excess of endo isomer was formed of major enantiomer *S* configuration. [c] 87% conversion by ^{1}H-NMR

On the other hand, the benzyl analogue compound **284**.HCl gave a product with an ee similar to that obtained with TsDPEN **64**.HCl and could not be recovered after the reaction (Table 29, Entry 6). Thus, compound **284**.HCl appeared to have hydrolysed back to the starting materials under the reaction conditions. This is most likely to be

due to its low stability as observed during the synthesis. At the same time, all of the silyloxy, hydroxy and alkoxy derivatives **278**, **282** and **283** respectively could be isolated back from the reaction and reused.

This difference in the stability of compounds **278**, **282**-**283** and **284** may be a result of the electron-withdrawing effect of the alkoxy and silyloxy groups. In order to confirm the stability of compound **278** under the reaction conditions, it was reacted with excess of acrolein and then analysed by ^{1}H-NMR. There was no change in the ^{1}H-NMR spectrum of the starting compound **278**, thus the cyclic aminal in compound **278** appears to be stable under the reaction conditions. Compound **278** gave complete conversion to product under optimised conditions by ^{1}H-NMR. However, due to the low boiling point of the resulting products, the yields were quite low.

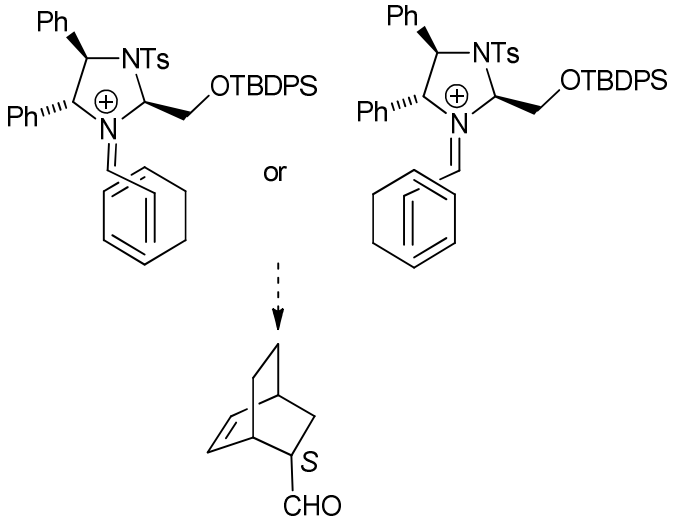
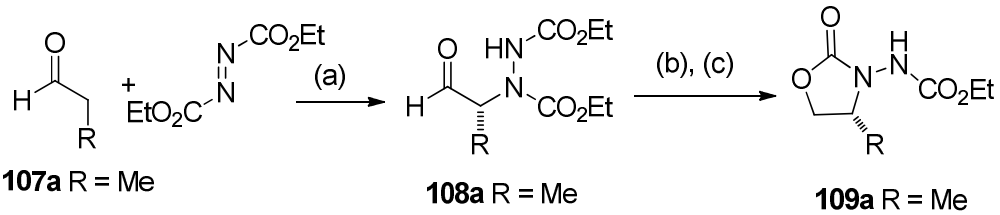


Figure 48: Diels-Alder reaction of 1,3-cyclohexadiene and acrolein using compound **278**.

To identify the configuration of the aldehyde product **293a**, the product (with 72% ee) obtained using compound **278**.HCl was reduced to the alcohol and the optical

rotation was compared with known literature values.[240] The alcohol was found to be present in the *S* configuration based on the optical rotation data, which also confirms the *S* configuration of the starting aldehyde **293a**. Thus, the addition reaction may take place from the less hindered side of the *E*-iminium cation transition state as shown in Figure 48.[118]

Compound **278** was used as a catalyst for the Michael addition of ketones to *trans*-β-nitrostyrene; the addition of dimethyl malonate to *trans*-β-nitrostyrene; and an aldol reaction. In each case however, no conversion was seen over. During the investigation of the catalytic activity of compound **278**, it exhibited high selectivity for the addition of aldehyde to DEAD. Compounds **278**, **282**-**284** and TsDPEN **64** were used as catalysts for the addition of aldehyde to DEAD in dichloromethane at room temperature (Scheme 52, Table 31). The resulting addition product **108a** may undergo a reversible reaction or be deprotonated at the α-position, resulting in decreased enantioselectivity. In order to overcome this problem, the addition product **108a** was reduced to its alcohol and then cyclised to form the stable oxazolidinone **109a** under basic conditions. This compound **109a** was used for chiral HPLC or GC to calculate the enantioselectivity.

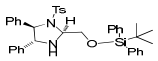
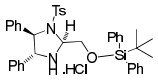
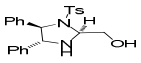
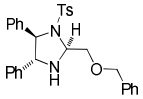


107a R = Me **108a** R = Me **109a** R = Me

Reagents and Conditions: (a) Catalyst (10 mol%), DCM,19-20 °C; (b) $NaBH_4$, MeOH, 20-21 °C, 30 min; (c) 0.5 N NaOH sol., 20-21 °C, 2 h

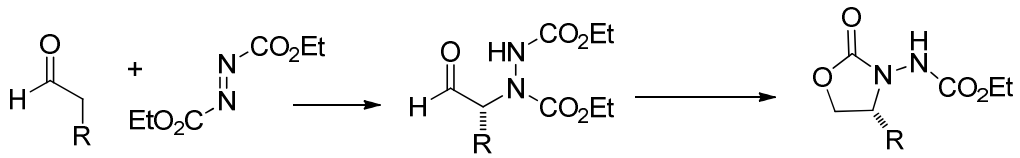
Scheme 52: Nucleophilic addition of propionaldehyde to DEAD using compounds **278**, **282**-**284** and TsDPEN **64**.

Table 31: Addition of propionaldehyde to DEAD using compounds **64**, **278**, and **282-283**.

Entry	Catalyst	R	Time[a]	% Yield[b]	%ee[c]
1	 **64**	Me	47 h	42%	33%(*R*)
2	 **278**	Me	14 h	55%	95% (*R*)
3	 **278**	Me	3 days	NC	
4	 **282**	Me	5 days	NC	
5	 **283**	Me	32h	46%	62% (*R*)

[a] The time is for completion for first addition step, [b] The % yields are calculated on basis of isolated product, NC = No conversion, [c] The enantiomeric excess is calculated from chiral GC data, major enantiomer *R*.

Compound **278** was selected for optimisation of the reaction conditions for the addition of aldehyde to DEAD due to the high selectivity shown in the initial study (Table 31). The reaction was carried out in different solvents such as dichloromethane, acetonitrile, toluene, hexane, ethyl acetate, dioxane, dichloroethane, but none of them gave faster conversion. The reaction without any solvent was found to be fast with the same selectivity using compound **278**.



107c R = *i*Pr **108c** R = *i*Pr **109c** R = *i*Pr

The addition reaction of propionaldehyde to DEAD was selected for earlier studies, but during the optimisation studies the reaction was found to be quite fast and difficult to monitor by ^{1}H-NMR. However, the reaction using isovaleraldehyde was

found to be suitable to monitor by ^{1}H-NMR and due to this reason isovaleraldehyde was selected for the optimisation of reaction conditions using compound **278**.

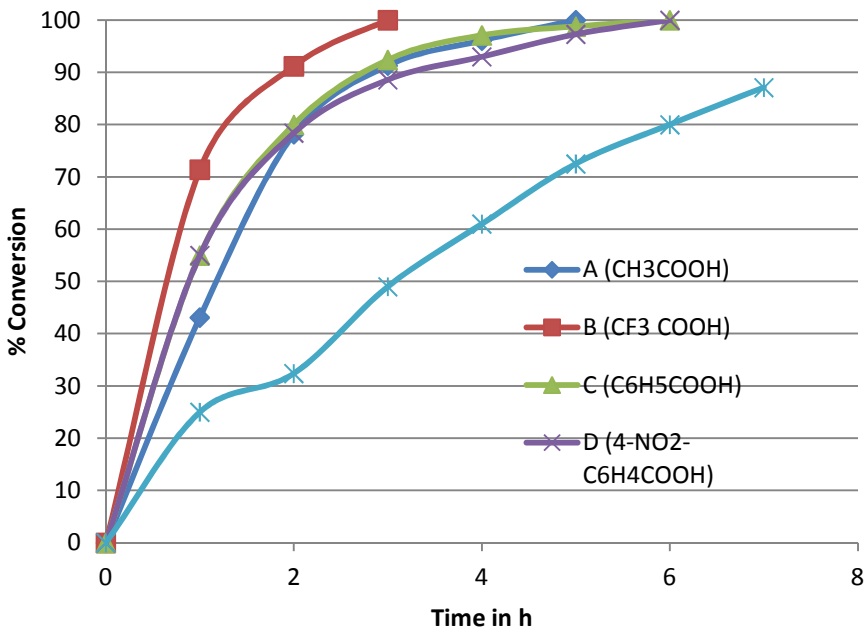


Figure 49: Addition of isovaleraldehyde to DEAD using compound **278**.

Conditions: compound **278** = 10 mol%, without acid or Acid = 10 mol%, aldehyde = 0.861 mmol, DEAD = 0.574, 20 ^{o}C. Followed by ^{1}H-NMR.

The addition of a catalytic amount of a range of acids with compound **278** was investigated for the addition of isovaleraldehyde to DEAD. The various effects on the rate of reaction are shown in Figure 49. Under the reaction conditions 10 mol% of compound **278** and 10 mol% of acid were used and conversion was calculated by taking ^{1}H-NMR at different time intervals. The acids used included acetic acid, benzoic acid, 4-nitro benzoic acid and all showed significant conversion with similar selectivity. While the reaction using trifluoroacetic acid was quite fast compared to the others, there was a drop in the enantioselectivity (Figure 50). The reaction with acetic acid was found to be good for both efficiency and selectivity.

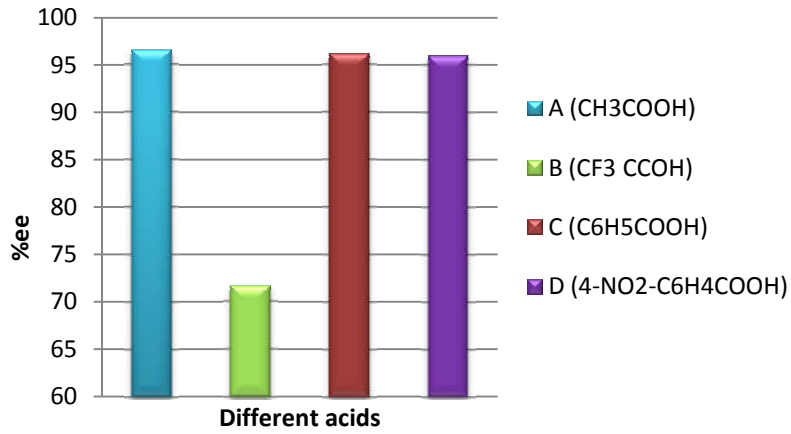


Figure 50: Addition of isovaleraldehyde to DEAD using compound **278**.

Conditions: compound **278** = 10 mol%, Acid = 10 mol%, aldehyde = 0.861 mmol, DEAD = 0.574, 20 ^{o}C. Followed by ^{1}H-NMR and chiral GC.

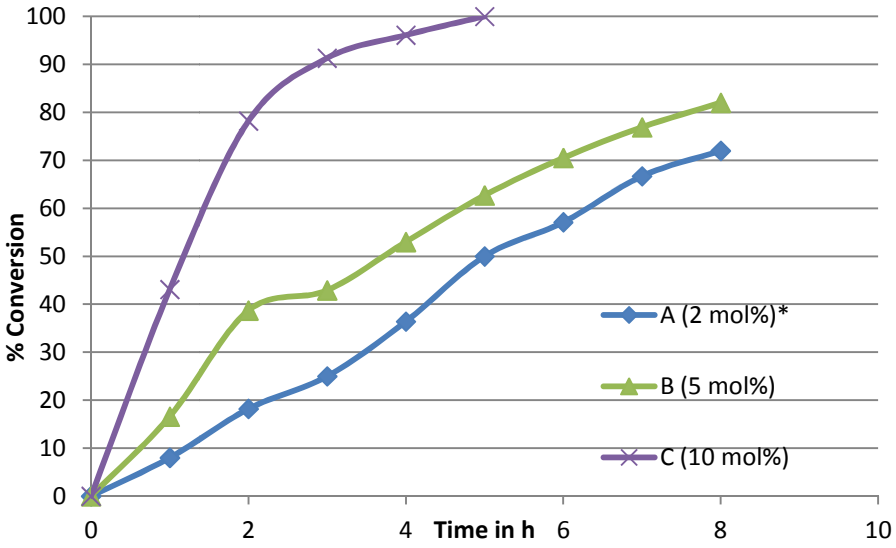


Figure 51: Addition of isovaleraldehyde to DEAD using compound **278**.

Conditions: compound **278**= 2, 5 and 10 mol%, AcOH = 10 mol%, aldehyde = 0.861 mmol, DEAD = 0.574, 20 ^{o}C. Followed by ^{1}H-NMR.* In reaction with 2 mol% catalyst loading side reaction of DEAD was observed.

The catalyst loading was optimised using 2, 5 and 10 mol% of compound **278** under the neat reaction conditions with 10 mol% of acetic acid at room temperature (Figure

51). With a 2 mol% catalyst loading, decomposition of DEAD was observed, while a 5 mol% loading was found to be quite slow compared to 10 mol%. Thus, 10 mol% loading of compound **278** was required for the optimal rate of reaction.

The reactions were carried out without any acid and with 5, 10, 15, 20 mol% acetic acid to see the effect of acid in the catalytic activity of compound **278** for the addition reaction, (Figure 52). Under the reaction conditions, it was found that the reaction was much slower without acetic acid and that 10 mol% of acetic acid is optimal for a faster rate of reaction. Using 15 and 20 mol% of acetic acid gave similar conversions to those achieved using 10 mol% of acetic acid and so offers no improvement or benefits to the reaction.

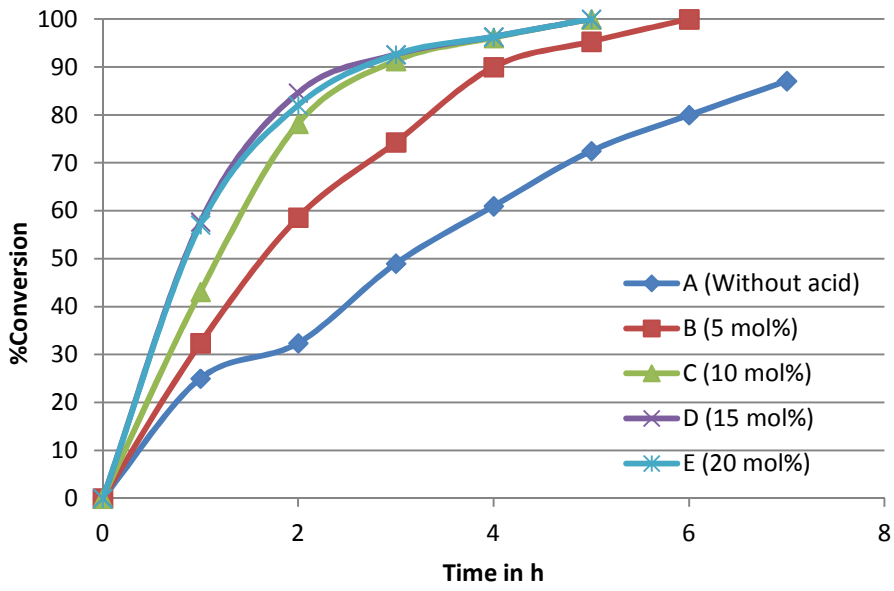


Figure 52: Addition of isovaleraldehyde to DEAD using compound **278**.

Conditions: compound **278** = 10 mol%, Acid = 5, 10, 15 and 20 mol%, aldehyde = 0.861 mmol, DEAD = 0.574, 20 ^{o}C.

The addition reaction of isovaleraldehyde to DEAD using 10 mol% of compound **278** and 10 mol% of acetic acid was carried out at three different temperatures; 0-5

^{o}C, 22-23 ^{o}C and 40 ^{o}C. The reaction was found to be much slower at 0-5 ^{o}C with complete conversion for the first step requiring 24 h, while the reaction at 22-23 ^{o}C was completed in 4.5 h. Both temperature conditions showed similar enantioselectivity (97% ee). At 40 ^{o}C the reaction was much faster to give complete addition for the first step in 2.5 h, with the drop in ee to 93.4% compared to 97 % (Figure 53).

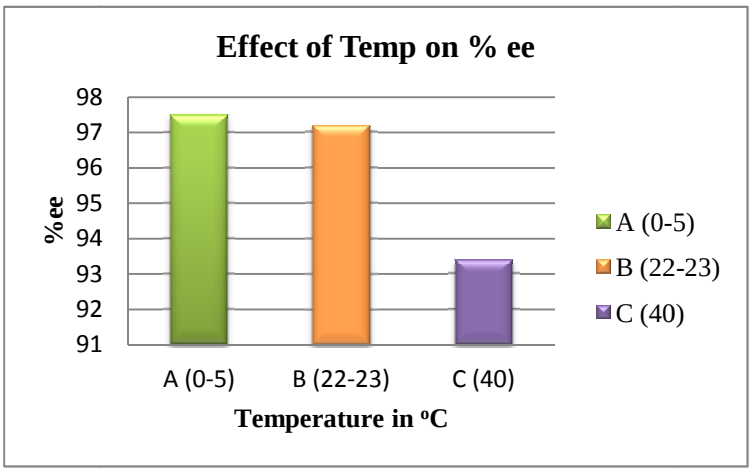
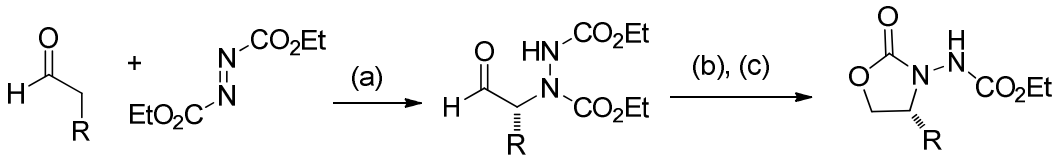


Figure 53: Addition of isovaleraldehyde to DEAD using compound **278**.

Conditions: compound **278** = 10 mol%, Acid = 10 mol%, aldehyde = 0.861 mmol, DEAD = 0.574, Temp = 0-5 ^{o}C, 22-23 ^{o}C and 40 ^{o}C.

For addition of the aldehyde to DEAD, the optimised conditions were found to be neat conditions, 10 mol% of catalyst and 10 mol% of acetic acid loading, at room temperature. Under the optimised conditions compounds **282**-**283** were again used as catalysts for the addition of propionaldehyde to DEAD (Scheme 53, Table 32).

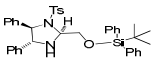
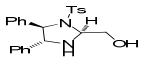
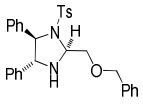
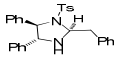


107a R = Me **108a** R = Me **109a** R = Me

Reagents and Conditions: (a) Catalyst (10 mol%), Acetic acid (10 mol%),19-20 °C; (b) $NaBH_4$, MeOH, 20-21 °C, 30 min; (c) 0.5 N NaOH sol., 20-21 °C, 2 h

Scheme 53: Nucleophilic addition of propionaldehyde to DEAD using compounds **64**, **278**, **282-284**.

Table 32: Addition of propionaldehyde to DEAD using different using compounds **64**, **278**, **282-284**.

Entry	Catalyst	R	Time[a]	% Yield[b]	%ee[c]
1	 **64**	Me	50 min	66%	49%
2	 **278**	Me	110 min	55%	95% (*R*)
3	 **282**	Me	31h	37%	61% (*R*)
4	 **283**	Me	50 min	66%	90% (*R*)
5	 **284**	Me	115 min	Crude	84%(*R*)

[a] The time is for completion for first addition step, [b] The % yields are calculated on basis of isolated product, [c] The enantiomeric excess is calculated from chiral GC data, major enantiomer *R*

The addition reaction using TsDPEN **64** was quite fast with a low selectivity under the optimised conditions (Table 32, Entry 1). The reaction using compound **278** was

completed in 110 min with high enantioselectivity of 95% ee (Table 32, Entry 2). The hydroxyl analogue **282** exhibited catalytic reactivity under optimised conditions with moderate selectivity (Table 32, Entry 3). Compounds **283** and **284** have also showed high reactivity and good enantioselectivity; 90% and 84% ee respectively (Table 32, Entries 4 & 5).

The formation of the product of *R* configuration using catalyst **278** suggests a reaction *via* an *E*-enamine transition state. The high enantioselectivity for the R enantiomer may be due to the addition taking place from the less hindered site as shown in Figure 54.[118]

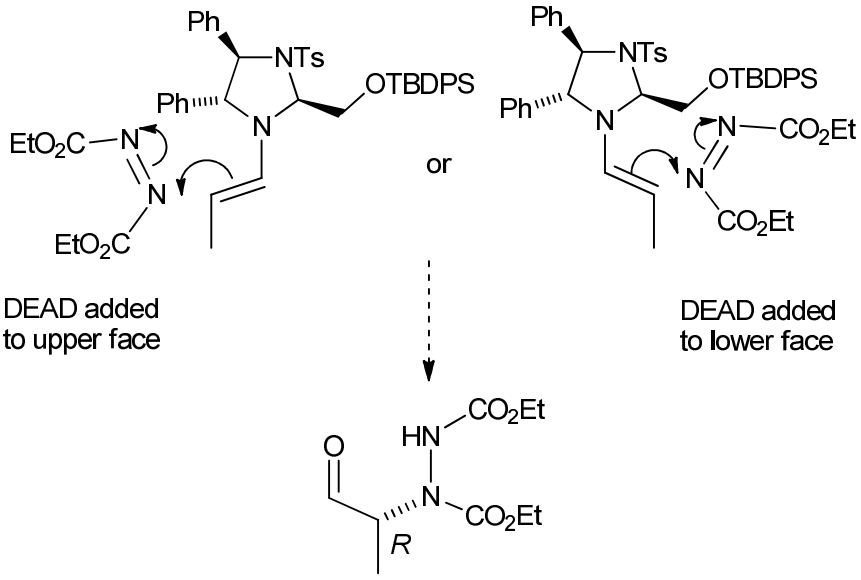


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Figure 54: Addition of DEAD to aldehyde using compound **278**.

Finally, the repeat additions of substrate (both with and without extra acid) were examined and this revealed that catalyst **278** continued to catalyse the addition with high enantioselectivity, although the reaction time increased with each addition (Figures 55 & 56).

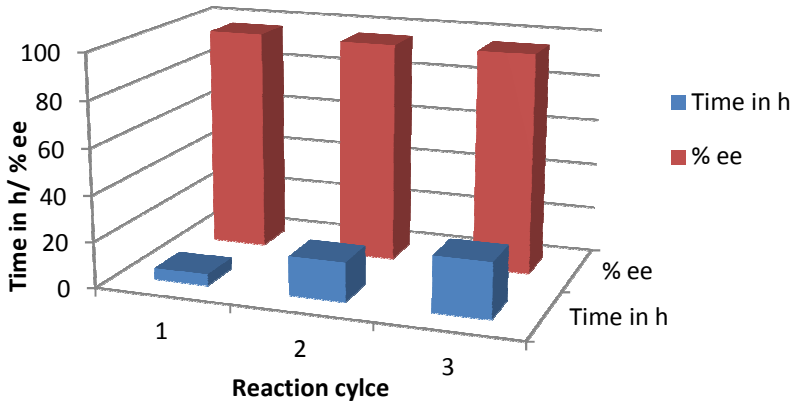


Figure 55: Effect of repeat addition of aldehyde, DEAD and acetic acid using compound **278** on rate of reaction and % ee.

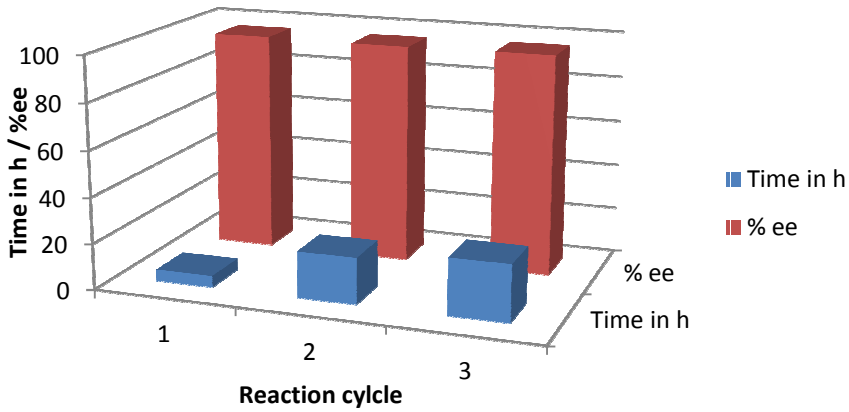


Figure 56: Effect of repeat addition of aldehyde and DEAD using compound **278** on rate of reaction and % ee.

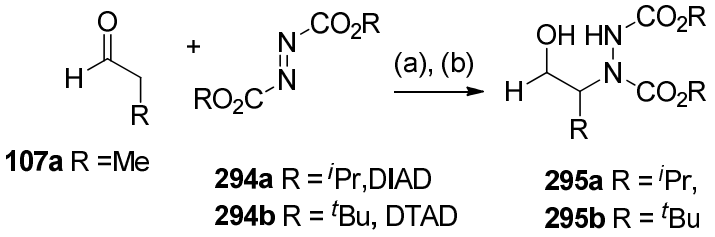
The lower reactivity and high enantioselectivity, suggests that catalyst inhibition may be taking place, rather than hydrolysis, since TsDPEN **64** was found to give a product of much lower ee. Whilst 100% conversion of DEAD (limiting reagent) to **108a** was observed by NMR, this product was not isolated because it was prone to racemisation. Instead, **108a** was reduced and cyclized to the configurationally stable

oxazolidinone **109a** in order to establish the ee. Since the reactions were followed by taking samples at intervals, the isolated yields were not recorded for these reactions.

Table 33: Addition of different aldehydes to DEAD using catalyst **278**.

Entry	R	Time[a]	% Yield[b]	%ee[c]
1	Me	110min	55%	95% (*R*)
2	Et	3h	65%	97% (*R*)
3	*i*Pr	4.5h	60%	96% (*R*)
4	Benzyl	4h	38%	84% (*R*)

[a] The time is for completion for first addition step, [b] The % yields are calculated on basis of isolated product, [c] The enantiomeric excess is calculated from chiral GC data, major enantiomer *R* .

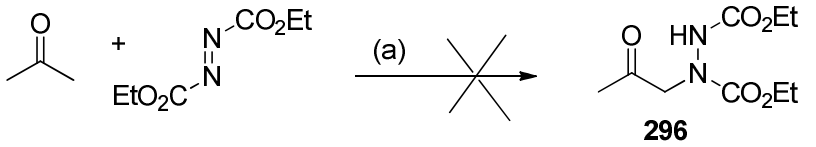


107a R =Me

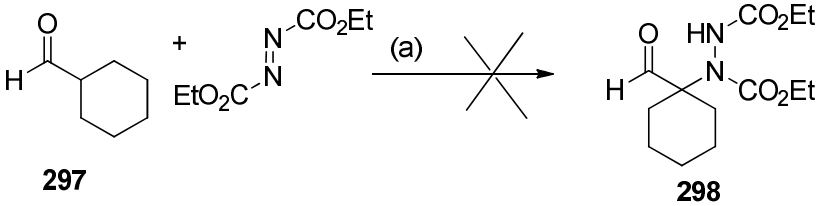
294a R = *i*Pr,DIAD
294b R = *t*Bu, DTAD

295a R = *i*Pr,
295b R = *t*Bu

Reagents and Conditions: (a) Catalyst **278** (10 mol%), Acetic acid (10 mol%),19-20 °C, 2-28 h; (b) $NaBH_4$, MeOH, 20-21 °C, 30 min;



296



297

298

Reagents and Conditions: (a) Catalyst **278** (10 mol%), Acetic acid (10 mol%),19-20 °C, 43-46 h;

Scheme 54: Addition of carbonyl compounds to azodicarboxylate.

The reaction was extended to alternative carbonyl substrates using compound **278** which gave mixed results. The addition of different aldehydes worked well, giving products with high enantioselectivities except for phenylpropionaldehyde with 84% ee (*R* enantiomer) (Table 33). The use of the DIAD **294a** and DTAD **294b** gave products in good yields (Scheme 54). Enantiomeric excesses were not determined in these cases. The addition reactions of acetone or formylcyclohexane to DEAD were unsuccessful using compound **278** (Scheme 54) even after stirring the reaction mixtures for 43-46 h.

In summary, the hydrochloride salt of compound **278** was found to be a good organocatalyst for the Diels-Alder reaction between 1,3-cyclohexadiene and acrolein with an enantioselectivity of 75% ee. The compound **278** was also shown good to exhibit high efficacy and selectivity as organocatalyst for the addition reaction of simple aldehydes to DEAD in the presence of catalytic amounts of acetic acid. The addition reaction of aldehyde to DEAD was found to be much faster using 10 mol% of compound **278** and same amount of acetic acid compared to the reaction without any acid. Thus, added acetic acid helps in formation of enamine intermediate between the compound **278** and aldehyde followed by providing proton during the addition of DEAD to the enamine. However, compound **278** was found to be less suitable for addition reaction of hindered aldehydes and ketones to DEAD.

2.3 Chiral Ru complexes for asymmetric transfer hydrogenation of ketones and imines

Compound **153** has shown high efficacy and selectivity for reduction of different aryl alkyl ketones and imines under asymmetric transfer hydrogenation conditions as discussed in section 1.4.7. The mechanism of asymmetric transfer hydrogenation of ketones is well established using compound **153** as discussed in section 1.4.4. The intermediates formed during catalytic cycles are 16 electron species **154** and ruthenium hydride **155** (Section 1.4.4., Figure 26). The hydride derivative **155** is the one of the intermediate in the transfer of hydrogen to the substrate.[176] An unexpected finding is that use of the same chiral complex for ketone and imine reduction resulted in different product enantiomers (Section 1.4.4., Figure 32).[173,188] To obtain more insight into the reaction, a number of research groups have carried out mechanistic studies using different hydrogen sources,[189] reduction using an Ru-H intermediate **155** with different acid[190] and molecular modelling as discussed in section 1.4.4. The outcome of all the studies indicates that ketone reduction is likely to involve a cyclic transition state *via* a concerted mechanism, whereas imine reduction appears to involve an ionic pathway.[177,180,189-190] In order to eliminate the possibility of involvement of an *N*-H bond in the reduction transition state, TsDPEN derivatives with two alkyl substituents on the basic nitrogen are required (Figure 57). Compound **299** can give a possible insight into the hydrogenation of ketones and imines because it will not be able to reduce the ketone group of the acetophenone due to lack of the -*N*H interaction required for six membered cyclic transition states. In contrast, it would be predicted that imine reduction will not be affected that much using compound **299** under similar conditions (as discussed in section 1.4.4).

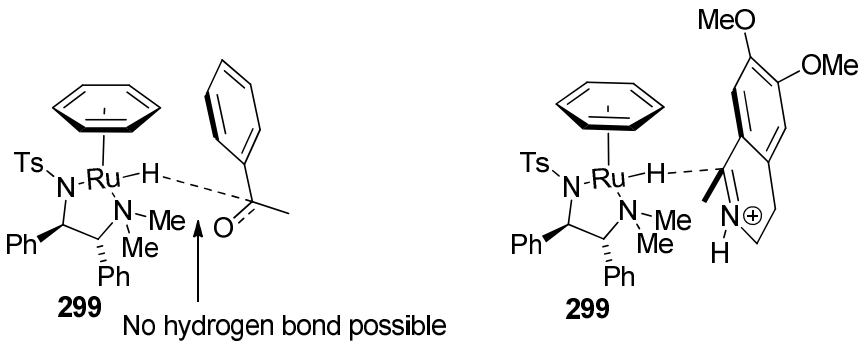
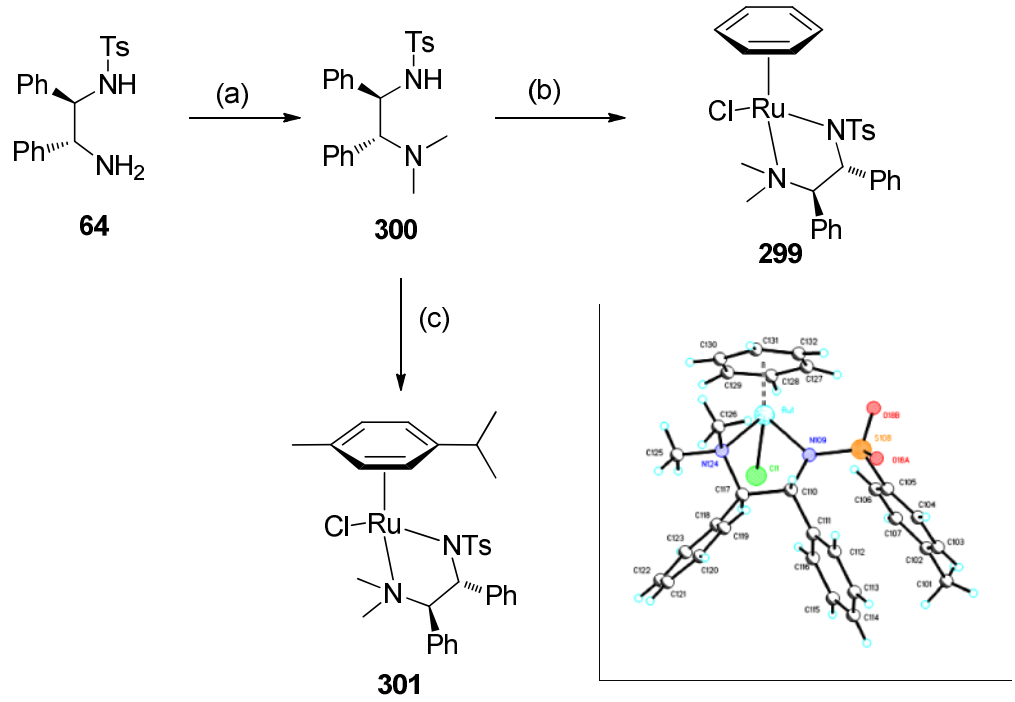


Figure 57: Proposed inhibition for ketone reduction using *N*,*N*-dimethyl-TsDPEN Ru catalyst.

2.3.1 Asymmetric transfer hydrogenation of ketones and imines using *N*,*N*-dimethyl-TsDPEN Ru catalyst

Complex **299** was synthesised as outlined in Scheme 55, starting from dimethyl TsDPEN **300**, itself prepared from TsDPEN **64**. The reductive amination was followed by complexation with benzene ruthenium(II)dichloride dimer. A similar compound formation was attempted using *p*-cymene ruthenium(II)dichloride dimer to afford compound **301**. Compound **301** was isolated and analysed by ^{1}H-NMR (shown in Figure 58) during the first attempt of the synthesis on a small scale (125 mg). A similar attempt on larger scale (325 mg) failed to give the required compound **301** in a pure form. These results suggest that for stability of compound **299** an unsubstituted arene ring is favoured.[182]

The crystal structure of the (*S*,*S*)-TsDPEN-Ru catalyst **153** showed the *R* configuration at Ru with δ-configurated five membered ring[176] and the crystal structure of (*R*,*R*) complex **193d** showed the *S* configuration at Ru.[191] In contrast the crystal structure of (*R*,*R*) compound **299** showed the *R* configuration at Ru with a change of angle of the oxygens of sulfonyl group, possibly due to the steric demand of the -*N*Me$_2$ group.



Reagents and Conditions: (a) HCHO (37% w/w), $NaBH_3CN$, MeOH, AcOH, 50 °C, 18 h, 100% ; (b) $[Ru(benzene)Cl_2]_2$, Et_3N, IPA, 80 °C, 1 h, 38%; (c) $[Ru(p\text{-cymene})Cl_2]_2$, Et_3N, IPA, 80 °C, 45 min, 23%

Scheme 55: Synthesis of *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzeneruthenium chloride **299**.

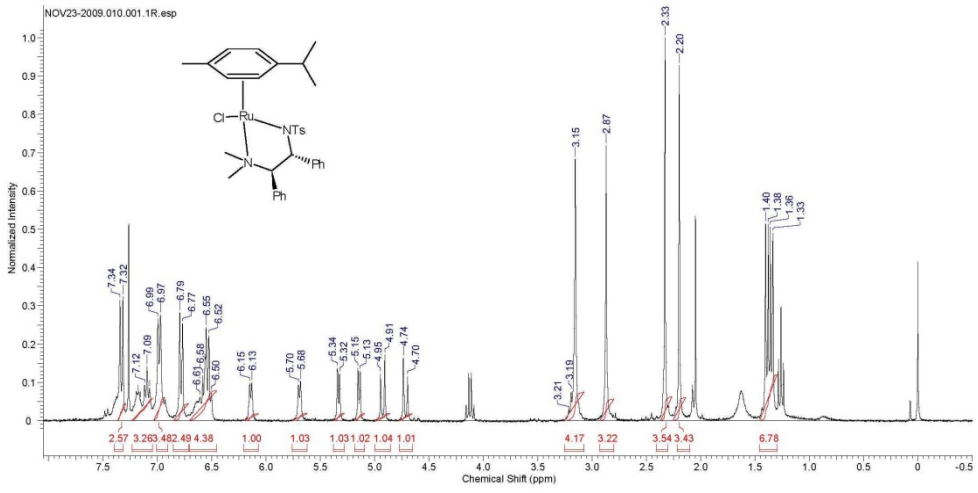
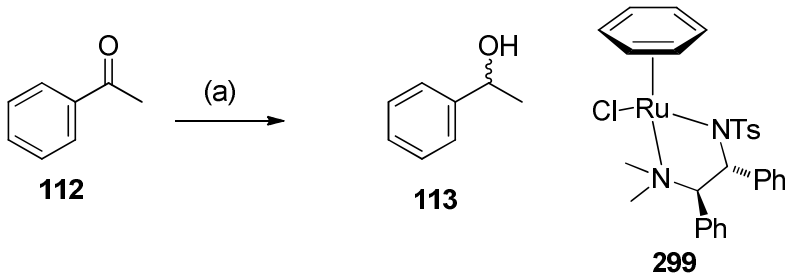


Figure 58: ^{1}H-NMR spectra of compound **301**

The asymmetric transfer hydrogenation using compound **153** is well studied with the formation of the amide compound **154** and the hydride compound **155** as discussed in section 1.4.4. The -*N*H is group is not present in compound **299.** Due to this compound **299** may not be able to form the amide and the hydrido derivatives similar to compound **153** under asymmetric transfer hydrogenation conditions. For similar compounds with lack of -*N*H group, there are reports using pressure hydrogenation and a silver salt to convert Ru-Cl to Ru-H.[191-194] On the basis of these results, compound **299** was used for pressure hydrogenation of ketone (acetophenone **112**) and imine **165** using different solvents and additives (Schemes 56 & 57, Tables 34 & 35) in the first attempt. As shown in Table 34, the level of acetophenone reduction was quite low in IPA. To remove the chloride ion from the complex, $AgSbF_6$ was used as an additive with complex **299**. However, reduction of acetophenone was reduced with addition of $AgSbF_6$. Addition of formic acid was attempted with $AgSbF_6$ for pressure hydrogenation.[191,194] In these tests, formic acid showed little promise in the solvents (Table 34, Entry 3). To compare the effect of $AgSbF_6$, the same reaction was attempted with only formic acid, which gave very low conversion for acetophenone (Table 34, Entry 4).[189-190]



112 **113** **299**

Reagents and Conditions: (a) Catalyst **299,** solvent/ additive, H_2 gas (30 bar), 30 ^oC, 21 h

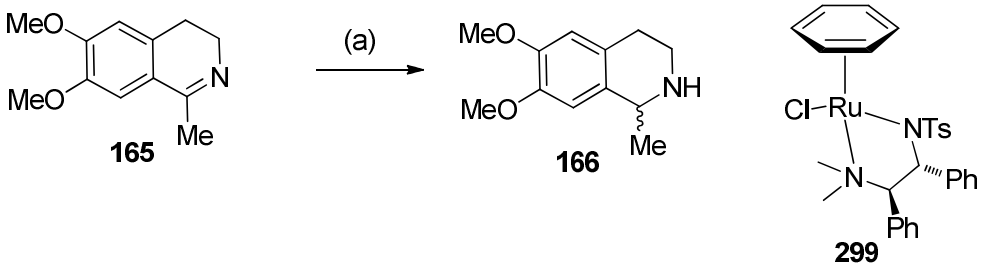
Scheme 56: Pressure hydrogenation of acetophenone using compound **299**.

Table 34: Pressure hydrogenation of acetophenone using compound **299**.

Entry	Additive [a]	Solvent	Time	% Conv[b]	% ee[c]
1		IPA	21h	18%	34% (*S*)
2	$AgSbF_6$	IPA	21h	9%	48% (*S*)
3	FA (3 eq)/ $AgSbF_6$	IPA	21h	29%	62% (*R*)
4	FA (3 eq)	IPA	21h	9%	0%

[a] additive $AgSbF_6$ = 4 mol%, [b] % conversion is calculated from chiral GC data, [c] The enantiomeric excess is calculated from chiral GC. Reaction conditions: catalyst **299** (1 mol%), H_2 gas = 30 bar, 30 ^oC, Time = 21 h.

At the same time, pressure hydrogenation of imine **165** was carried out using complex **299** under the similar conditions as used for acetophenone reductions (Scheme 57, Table 35). Reduction of imine **165** was quite low in IPA and even with added $AgSbF_6$ salt (Table 35, Entry 2).[191,194] The use of 1 eq of formic acid gave low conversion for the reduction of imine (Table 35, Entry 3). The use of excess formic acid (3 eq) gave high conversion with and without $AgSbF_6$ (Table 35, Entries 4-5).[189-190]



Reagents and Conditions: (a) Catalyst **271,** solvent/ additive, H_2 gas (30 bar), 30 ^oC, 21 h - 42 h.

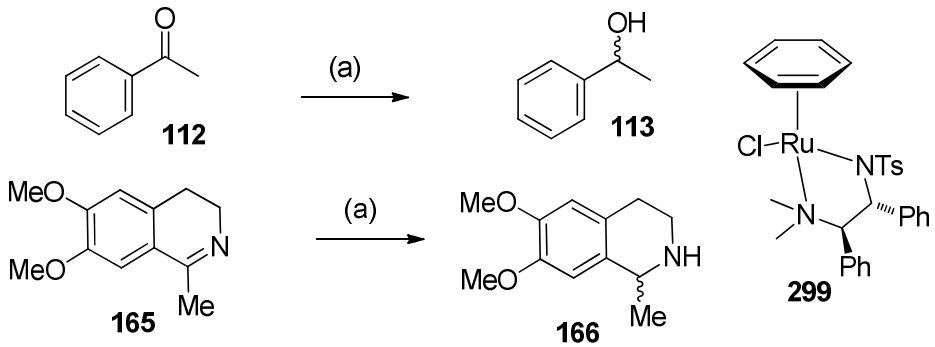
Scheme 57: Pressure hydrogenation of Imine **165** using compound **299**.

Table 35: Pressure hydrogenation of Imine **165** using compound **299**.

Entry	Additive [a]	Solvent	Time	% Conv[b]	% ee[c]
1		IPA	21h	3%	2%
2	$AgSbF_6$	IPA	21h	1.5%	2%
3	FA (1 eq)/ $AgSbF_6$	IPA	42h	42%	8%
4	FA (3 eq)/ $AgSbF_6$	IPA	21h	69%	2%
5	FA (3 eq)	IPA	21h	76%	4%

[a] additive $AgSbF_6$ = 4 mol%, FA:TEA = 2 eq, [b] % conversion is calculated from chiral GC data, [c] The enantiomeric excess is calculated from chiral GC. Reaction conditions: catalyst **299** (1 mol%), H_2 gas = 30 bar, 30 ^oC, Time = 21-42 h.

The pressure hydrogenation reaction of imine **165** was promising using complex **299** using 3 eq of formic acid (Table 35, Entry 5). The reduction of acetophenone and imine was also carried out using FA:TEA using complex **299** (Scheme 58). This gave quite low conversion in FA:TEA and even with added $AgSbF_6$ required up to 4 days (Table 36, Entries 1-2) for transfer hydrogenation of acetophenone.



Reagents and Conditions: (a) Catalyst **299**, FA:TEA(5:2), solvent/ additive, 30 ^oC, 19 h - 5 days.

Scheme 58: Asymmetric transfer hydrogenation of acetophenone using compound **299**.

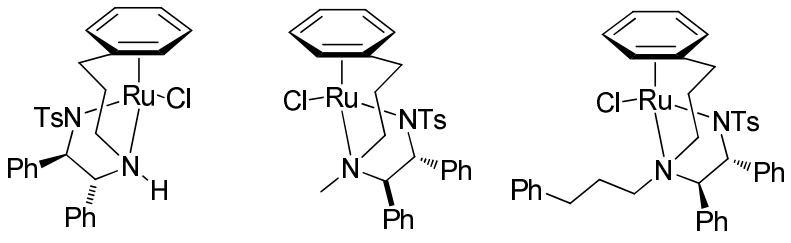
Table 36: Asymmetric transfer hydrogenation of Imine 62 using FA:TEA (5:2) compound **299**.

Entry	Substrate	Solvent/Additive[a]	Time	% Conv[b]	% ee[c]
1	**112**		21h	0.6%	0%
			4days	1.1%	0%
2	**112**	$AgSbF_6$	5 days	1.5%	17%
3	**165**		19h	36%	17% (*S*)
			45h	71%	24% (*S*)
			5 days	91%	18% (*S*)
4	**165**	CH_3CN	22h	7%	4%
			3 days	9%	0%
5	**165**	DCM	22h	8%	9% (*S*)
			3 days	12%	11% (*S*)
6	**165**	DMF	22h	12%	0%
			3 days	18%	15% (*S*)
7	**165**	MeOH	22h	6%	0%
			3 days	32%	0%
8	**165**	IPA	22h	9%	11% (*S*)
			69h	16%	10% (*S*)
9	**165**	EtOAc	22h	16%	5%
			69h	30%	0%

[a] additive $AgSbF_6$ = 4 mol%, [b] % conversion is calculated from chiral GC data, [c] The enantiomeric excess is calculated from chiral GC. Reaction conditions: catalyst **299** (1 mol%), FA:TEA, 30 ^oC, Time = 19h – 5 days.

The transfer hydrogenation of acetophenone using compound **299** was very slow under the different conditions used herein (Schemes 56 & 58, Tables 34 & 36). These results can be compared to the initial predictions of low reactivity of compound **299** for ketone reduction as shown in Figure 57. While for reduction of imine **165**, compound **299** gave 91 % conversion in 4 days using FA:TEA (Scheme 58, Table 36, Entry 3). In order to improve the rate of reduction for the imine, different solvents were investigated for the transfer hydrogenation including CH_3CN, DCM, DMF, MeOH, IPA, EtOAc. None of the solvents gave an improvement in the required conversion, indeed the reduction became slower in the presence of any of the solvents used (Table 36, Entries 4-9). Compound **299** was reacted with FA:TEA in $CDCl_3$ in the NMR tube to detect the hydride formation by ^{1}H-NMR. Compound **299** exhibited a hydride formation at δ -5.3 ppm, which was quite promising. The slow catalytic reactivity of compound **299** for reduction of imine **165** may depend on different factors such as stability of the complex, formation of the hydride, transfer of the hydride to the substrate.

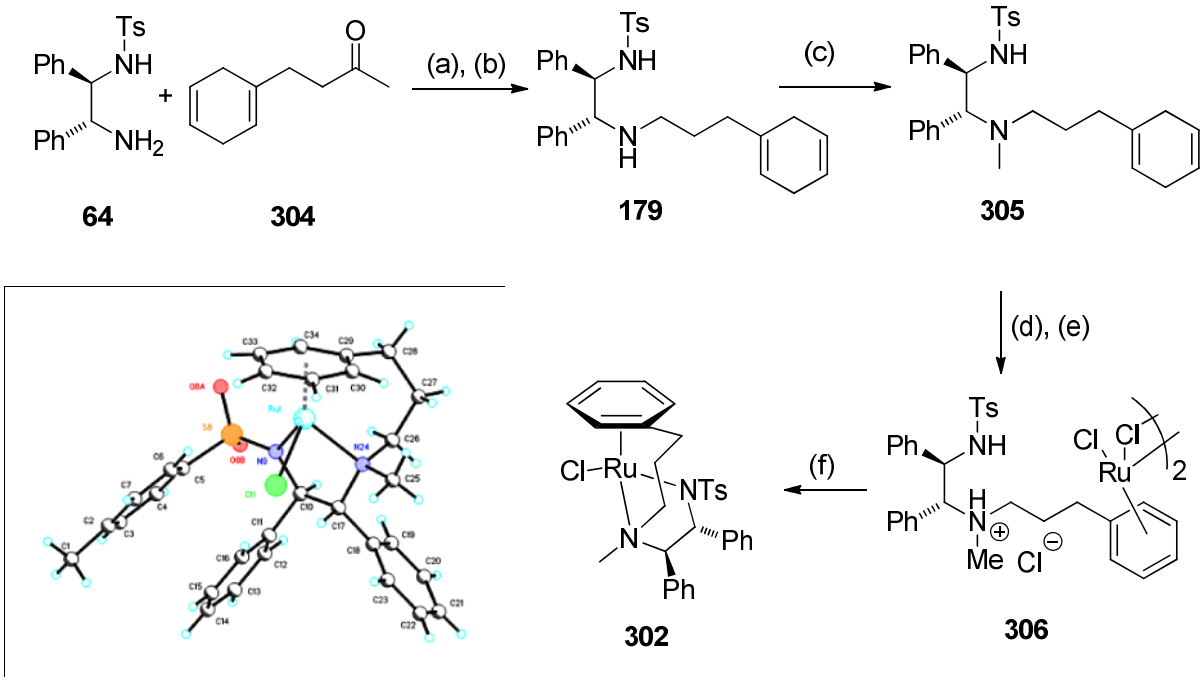
2.3.2 Asymmetric transfer hydrogenation of ketones and imines using *N*-alkylated Ru-3C-tethered catalysts



181 **302** **303**

Figure 59: *N*-alkylated analogues of Ru-3C-tethered complex **181**.

The next step was to form more stable and active complexes for imine reduction. The Ru-3C-tethered catalyst **181** has exhibited high efficiency and selectivity for transfer hydrogenation as discussed in section 1.4.6. *N*-Alkylated analogues of Ru-3C-tethered catalysts **302** and **303** were selected to synthesise and study for transfer hydrogenation (Figure 59).

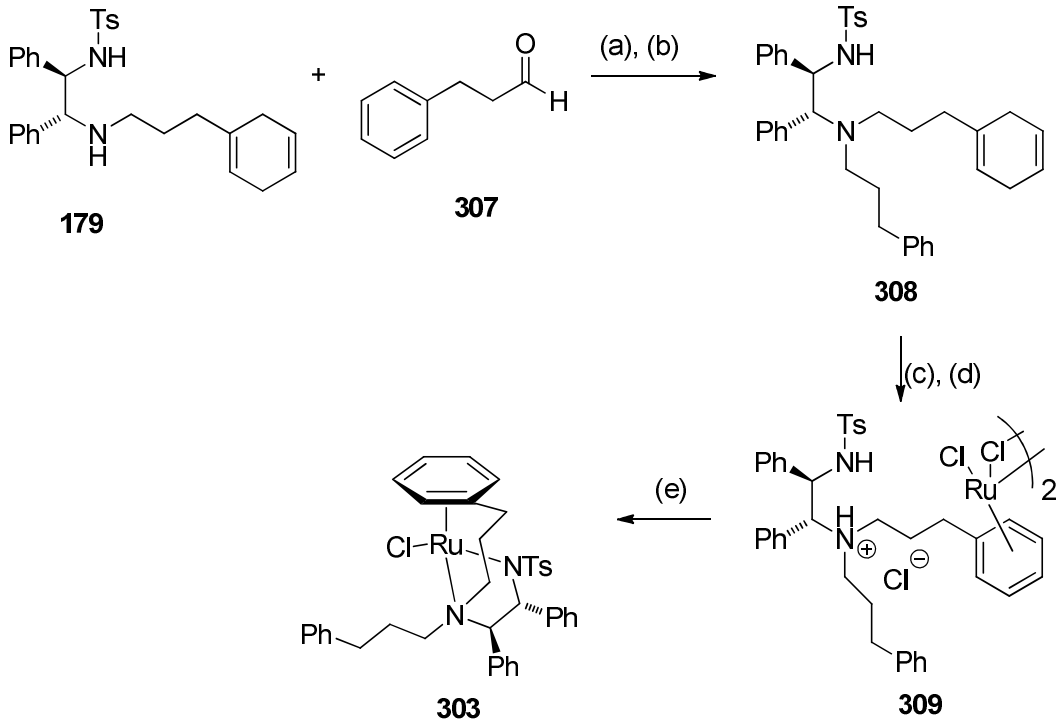


Reagents and Conditions: (a) dry MeOH, MS 4Å, AcOH, 20 °C, 2.5 h; (b) $NaBH_3CN$, 20 °C, 48 h, 78%; (c) dry MeOH, HCHO (37% aq soln), AcOH,50 °C,16 h, 73%; (d) HCl (2M in Et_2O), dry DCM, 15 min; (e) $RuCl_3$. $3H_2O$, EtOH, 78 °C, 16 h, 50%; (f) NEt_3, IPA, 80 °C, 1 h, 70%.

Scheme 59: Synthesis of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methylamino)]-4-methylbenzenesulfonamide}ruthenium chloride monomer (**302**).

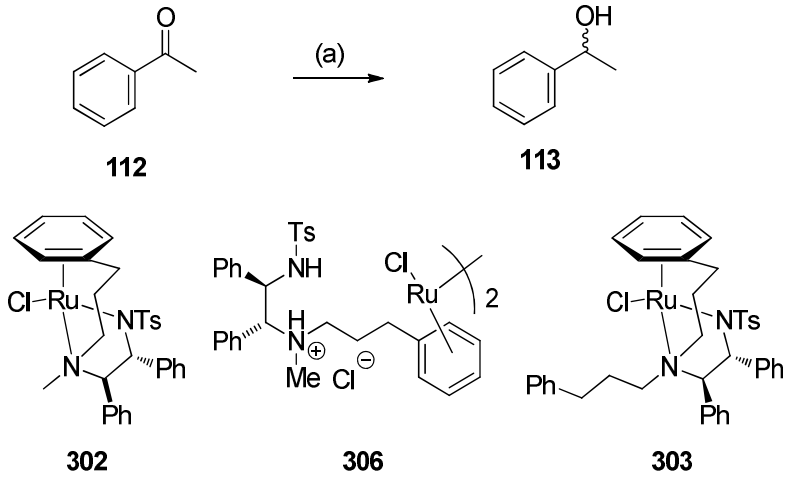
Complex **303** was synthesised as outlined in Scheme 59.[205] The reductive amination of TsDPEN **64** with aldehyde **304** resulted in the formation of compound **179**, which was subjected to a second reductive amination with formaldehyde to give the *N*-methyl derivative **305**. Compound **305** was converted into a hydrochloride salt and

reacted with ruthenium trichloride to give dimer **306**, which was converted into monomer **302** by using triethylamine in IPA. The crystal structure of (*S*,*S*)-Ru catalyst **181** showed the *R* configuration at Ru[205] whereas in contrast the crystal structure of (*R*,*R*) compound **302** showed *R* configuration with a change of angel of the oxygen of the sulfonyl group due to -*N*Me group, which is similar to the crystal structure of compound **299**. Similarly, complex **303** was synthesised as outlined in Scheme 60. Compound **308** was synthesised by reductive amination of compound **179** with phenyl propionaldehyde **307**. The hydrochloride salt of compound **308** was then reacted with ruthenium trichloride to give the dimer **309**, which was then converted into the monomer **303** by using TEA in IPA.



Reagents and Conditions: (a)dry MeOH, MS 4Å, AcOH, 20 °C, 4 h; (b) $NaBH_3CN$, 50 °C, 22 h, 55%; (c) HCl (2M in Et_2O), dry DCM, 15 min; (d) $RuCl_3.3H_2O$, EtOH, 78 °C, 16 h, 67%; (e) NEt_3, IPA, 80 °C, 1 h, 49%.

Scheme 60: Synthesis of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer (**303**)



Reagents and Conditions: (a) Catalyst, FA:TEA (5:2), solvent, 30 ^{o}C, 18 h - 8 days

Scheme 61: Asymmetric transfer hydrogenation of acetophenone using compounds **302**, **306** and **303**.

Table 37: Asymmetric transfer hydrogenation of acetophenone using FA:TEA (5:2) compounds **302**, **306** and **303**.

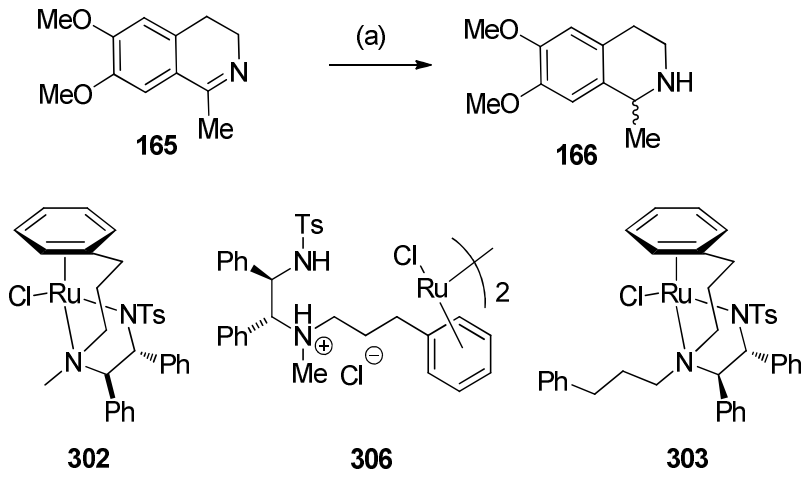
Entry	Catalyst	Time	% Conv[a]	% ee[b]
1	(*S*,*S*) tethered-*N*Me **302**	18h	6%	73% (*R*)
2	(*R*,*R*) tethered-*N*Me dimer **306**	45h	13%	74% (*R*)
		2 days	18%	67% (*S*)
		8 days	60%	67% (*S*)
3	(*R*,*R*) tethered-*N*$(CH_2)_3$Ph **303**	24h	11%	70% (*R*)
		4 days	17%	36% (*R*)

[a]% conversion is calculated from chiral GC data, [b]The enantiomeric excess is calculated from chiral GC. Reaction conditions: catalyst **302/306/303** (1 mol%), FA:TEA, 30 ^{o}C, Time = 18h – 8 days

Compounds **302**, **306** (dimer) and **303** were used for asymmetric transfer hydrogenation of acetophenone and imine **165** using FA:TEA (Scheme 61, Table 37). Compound **302** gave very low (6%) conversion for reduction of acetophenone (Table 37, entry 1,). The reduction using dimer **306** was also quite slow with 18% conversion after 2 days, the reaction was left running for a long time (up to 8 days) to achieve 60% conversion (Table 37, Entry 2). Similarly, a low conversion was obtained for the reduction of acetophenone using compound **303** (Table 37, Entry 3). These results confirm the necessity of the -*N*H on the basic nitrogen atom for reduction of a ketone group.

Similarly, asymmetric transfer hydrogenation of imine **165** was carried out using compounds **302**, **306** (dimer) and **303** (Scheme 62, Table 38). Compound **306** (dimer) gave high conversion (92%) in 20 h (Table 38, Entry 1). The monomer, compound **302** also gave 91% conversion in 20 h for imine reduction (Table 38, Entry 2), which was much faster compared to the reduction of acetophenone (7% after 20 h). Compound **302** was studied using different solvents such as MeOH, CH_3CN, IPA to see the effect on imine reduction. But none of the solvents affected the catalytic activity of compound **302** for reduction; all gave ~95% conversion over a period of 20 h (Table 38, Entries 3-5). Thus, compound **302** was a stable and effective catalyst for imine reduction.

Compound **303** gave a good conversion for imine reduction compared to complex **299**, but not as good as with compound **302** (Table 38, Entry 6), which may be due to the bulkier *N*-alkyl group. Compound **302** was analysed for hydride formation using FA:TEA in $CDCl_3$. Compound **302** has exhibited a Ru-H peak in NMR at δ -5.4 ppm.



Reagents and Conditions: (a) Catalyst, FA:TEA (5:2), solvent, 30 ^{o}C, 19 h - 5 days

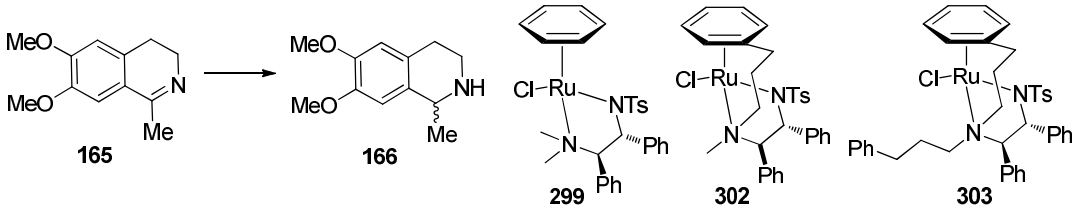
Scheme 62: Asymmetric transfer hydrogenation of Imine **65** using compounds **302**, **306** (dimer) and **303**.

Table 38: Asymmetric transfer hydrogenation of Imine **165** using compounds **302**, **306** (dimer) and **303**.

Entry	Catalyst	Solvent	Time	% Conv[a]	% ee[b]
1	(*R*,*R*) tethered-*N*Me dimer **306**		20h	92%	12% (*S*)
2	(*S*,*S*) tethered-*N*Me **302**		16.5h	95%	27% (*R*)
			20h	97%	24% (R)
3	(*R*,*R*) tethered-*N*Me **302**	MeOH	20h	95%	8% (*S*)
4	(*R*,*R*) tethered-*N*Me **302**	CH_3CN	20h	95%	21% (*S*)
5	(*R*,*R*) tethered-*N*Me **302**	IPA	20h	97%	14% (*S*)
6	(*R*,*R*) tethered-*N*$(CH_2)_3$Ph **303**		24h	95%	7% (*S*)

[a] % conversion is calculated from chiral GC data, [c] The enantiomeric excess is calculated from chiral GC. Reaction conditions: catalyst **302**/**306**/**303** (1 mol%), FA:TEA, 30 ^{o}C, Time = 19h – 5 days

A comparative study of compounds -*N*Me$_2$ **299**, tethered-*N*Me **302** and tethered-*N*-(CH$_2$)$_3$Ph **303** was carried out for asymmetric transfer hydrogenation of imine (Figure 60). The independent reactions were monitored by chiral GC for the conversion at different time intervals. Compound **302** gave quite good conversion for imine reduction. Compound **303** was slower compared to compound **302** over the reaction time. However, compound **299** was much slower compared to compounds **302** and **303** as observed earlier. Compounds **299**, **302** and **303** were compared with each other for the reduction of acetophenone and imine. But of more interest is how they compare with their -*N*H analogues for reduction under similar conditions.



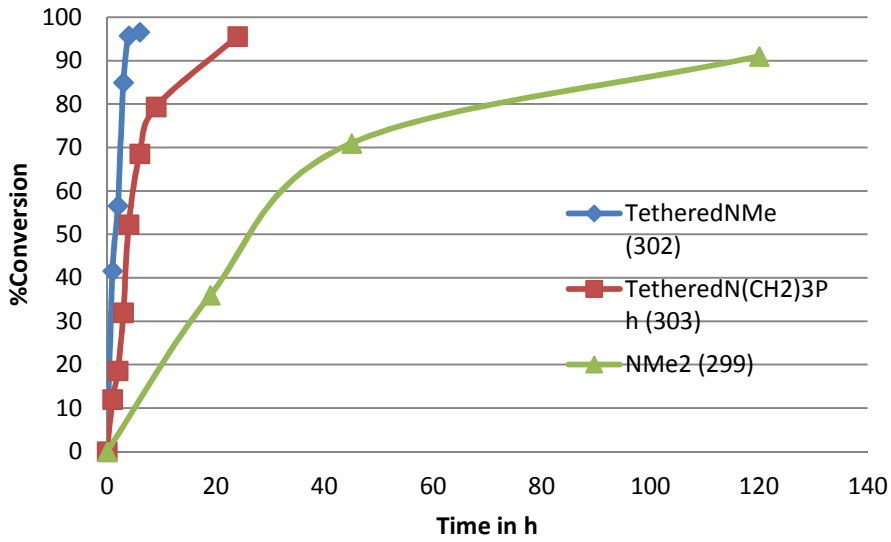


Figure 60: Asymmetric transfer hydrogenation of imine **165** using compounds **299**, **302** and **303**. **Conditions:** FA/TEA=5:2, [Imine]=0.5 M, 30 ^{o}C, S/C = 100. Followed by chiral GC.

2.3.3 Comparative studies for asymmetric transfer hydrogenation of ketones and imines using NMR

From earlier studies in the Wills group, experimental data for the reduction of ketones and imines was published for complexes **193** and **193a**.[195] Both compounds **193** and **193a** gave high conversion and enantioselectivity for reduction of acetophenone using FA:TEA (5:2). They gave high conversion and moderate enantioselectivity for reduction of imine **136** using FA:TEA(5:2). Complex **299** can be compared with compounds **193** and **193a** by repeating the reduction of ketone and imine under the similar conditions as published (Figure 61).[195]

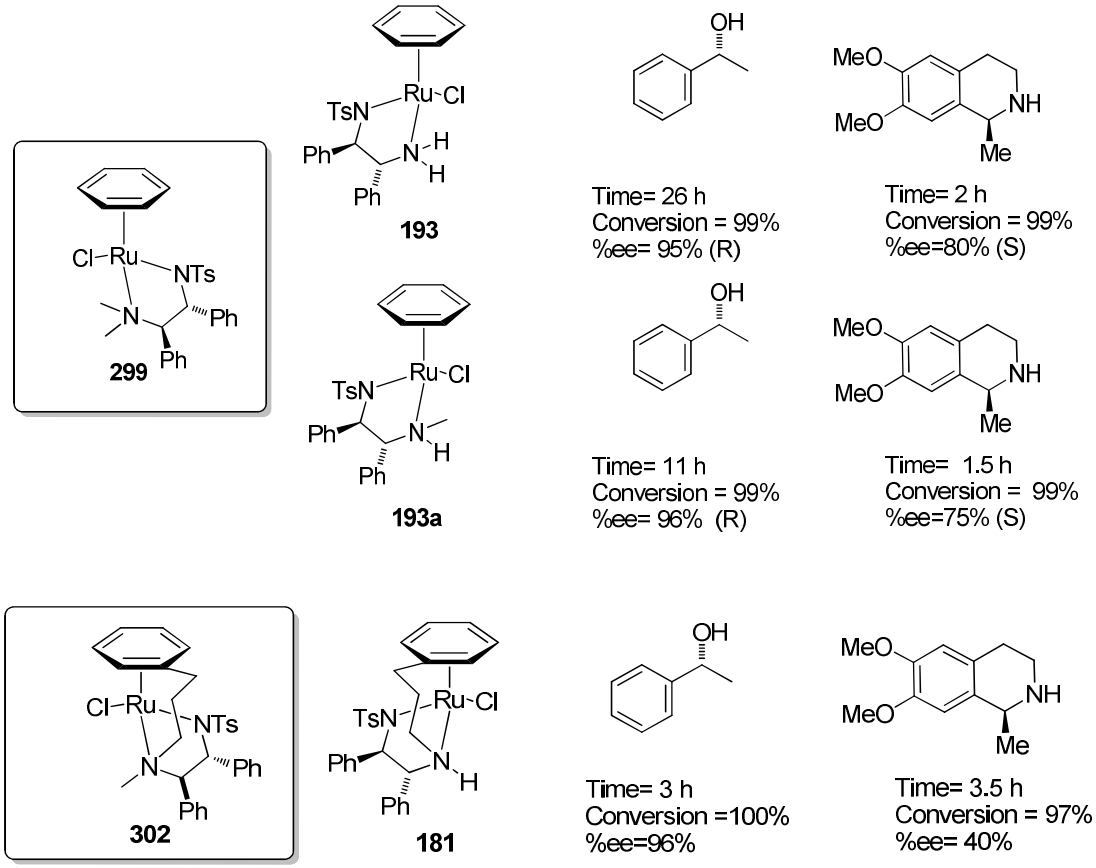


Figure 61: Comparison of compounds **299** and **302** with literature compounds **193-193a** and **181** for asymmetric transfer hydrogenation of acetophenone **112** and imine **165**.

Similarly, compound **302** can be compared with Ru-3C-tethered catalyst **181**, a highly efficient and selective catalyst for the acetophenone reduction (Figure 61).[205] The results obtained by this comparative study can be useful to explain the overall effect of *N*-alkylated compounds **299** and **302** on the reduction of ketone and imines compared to compounds **193**, **193a** and **181**.

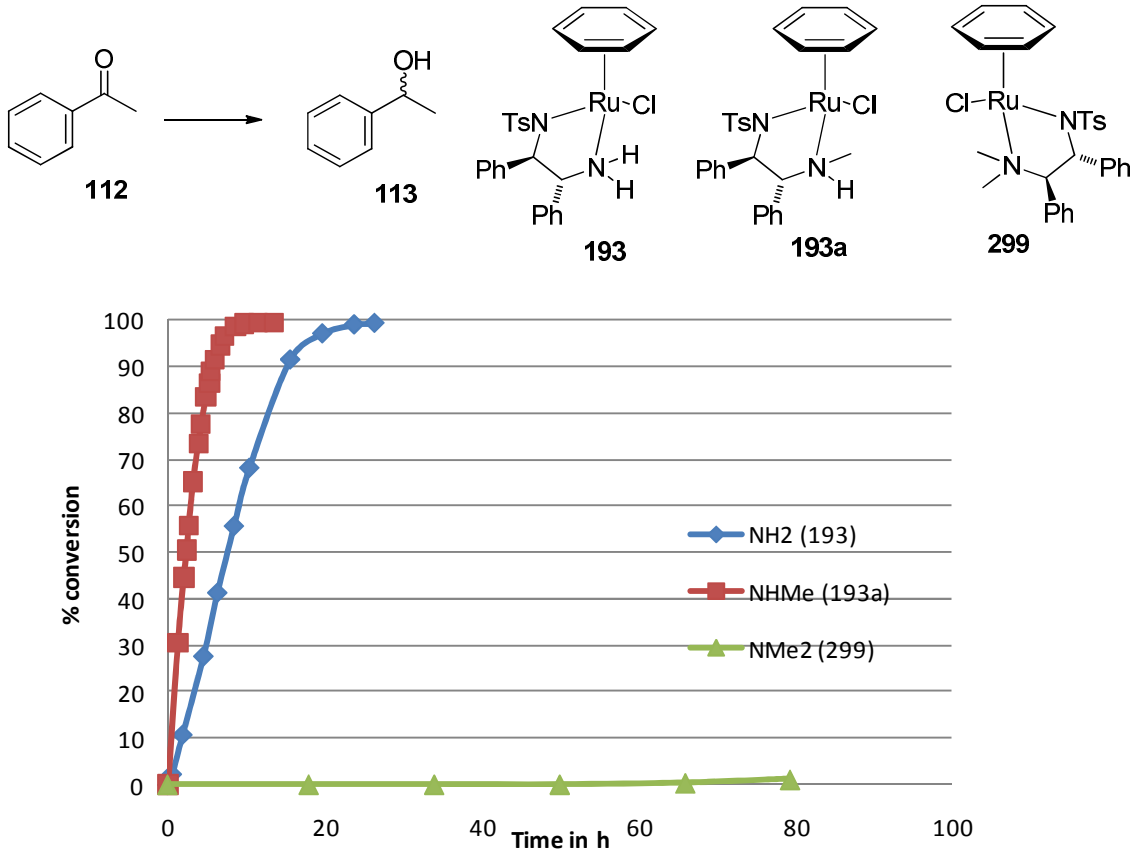
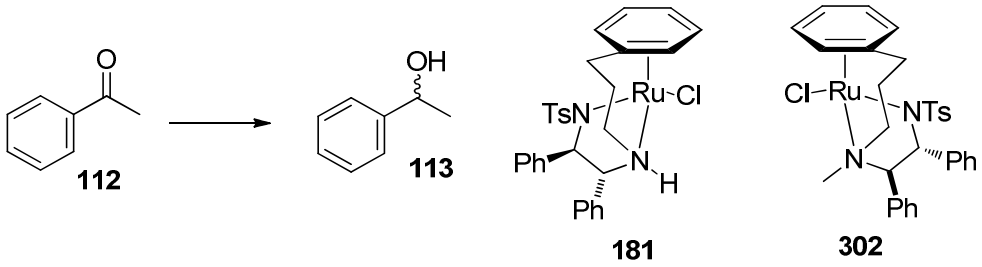


Figure 62: Asymmetric transfer hydrogenation of acetophenone **112** using compounds **193**, **193a** and **299**. **Conditions:** FA/TEA=5:2, [Ketone]=0.86 M, 25 ^{o}C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

The data for ketone reductions with complexes **193** and **193a** was compared with complex **299** data for reduction of acetophenone using 400MHz NMR (Ozric) by taking ^{1}H-NMR at different time intervals. Complex **193a** gave complete conversion in less time than compound **193** for the transfer hydrogenation of acetophenone as

shown in Figure 62. However, complex **299** was found to be much slower compared to both compounds **193** and **193a** for reduction of acetophenone under identical reaction conditions. Complexes **181** and **302** were also compared for the reduction of acetophenone under the similar conditions (Figure 63). Complex **181** was found to be much faster compared to complex **302** for acetophenone reduction.



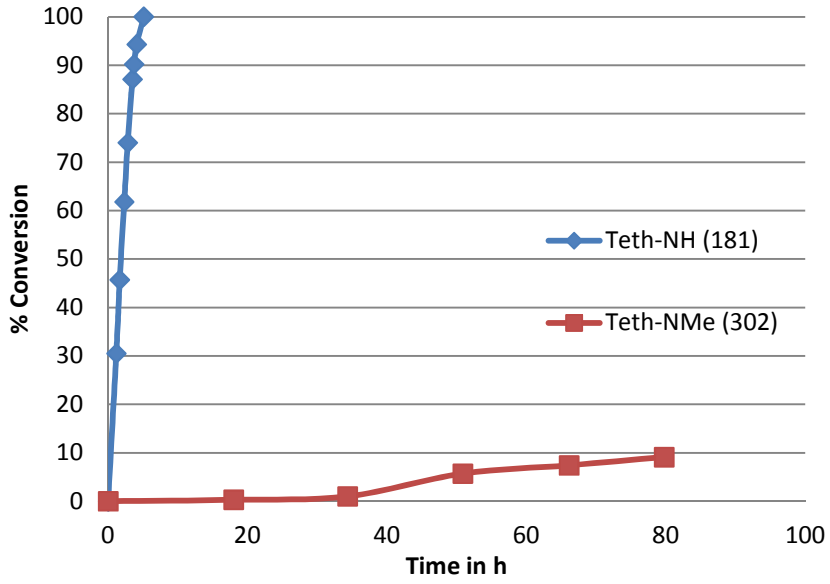


Figure 63: Asymmetric transfer hydrogenation of acetophenone **112** using compounds **181** and **302**. **Conditions:** FA/TEA=5:2, [Ketone]=0.86 M, 25 ^{o}C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

These results show that the -*N*H group on the basic nitrogen atom is required for ketone reduction. Compounds **299** and **302** which lack the -*N*H gave quite poor conversion for the reduction of ketones. In the same way, data for imine reductions

with complexes **193** and **193a** were compared with complex **299** data for imine reduction using 400MHz NMR (Ozric) by taking ^{1}H-NMR spectra at different time intervals. Complexes **193** and **193a** were much faster compared to compound **299** for reduction of imine under identical conditions (Figure 64).[195]

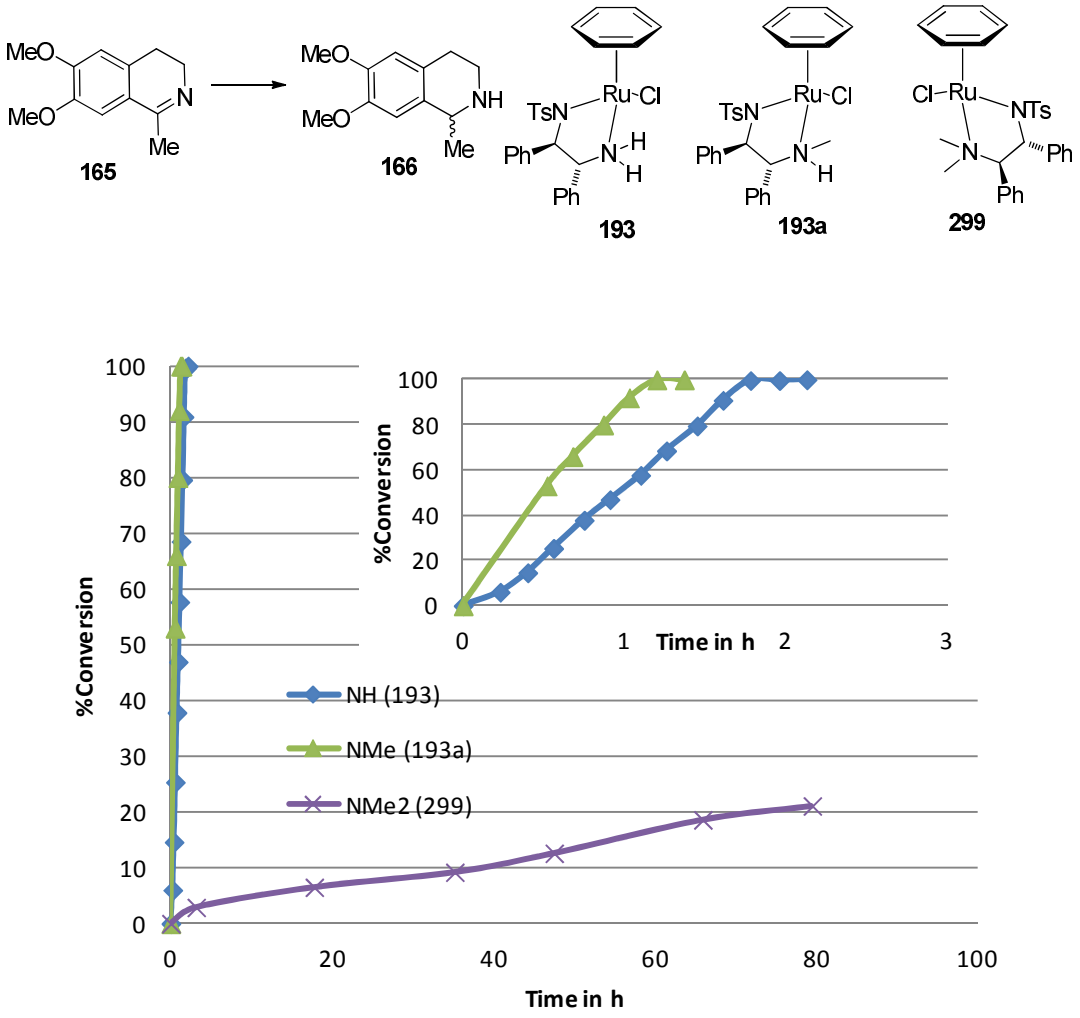


Figure 64: Asymmetric transfer hydrogenation of imine **165** using compounds **193**, **193a** and **299**. **Conditions:** MeCN, FA/TEA=5:2, [Imine]=0.45 M, 25 ^{o}C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

Compound **302** showed a steady increase in reduction over the period of the reaction, but was quite slow compared to compound **181** (Figure 65). Both compounds **299**

and **302** gave conversions for transfer hydrogenation of imines compared to ketones in the comparative study, although for imine reduction conversion was much slower compared to compounds **193**, **193a** and **181**.

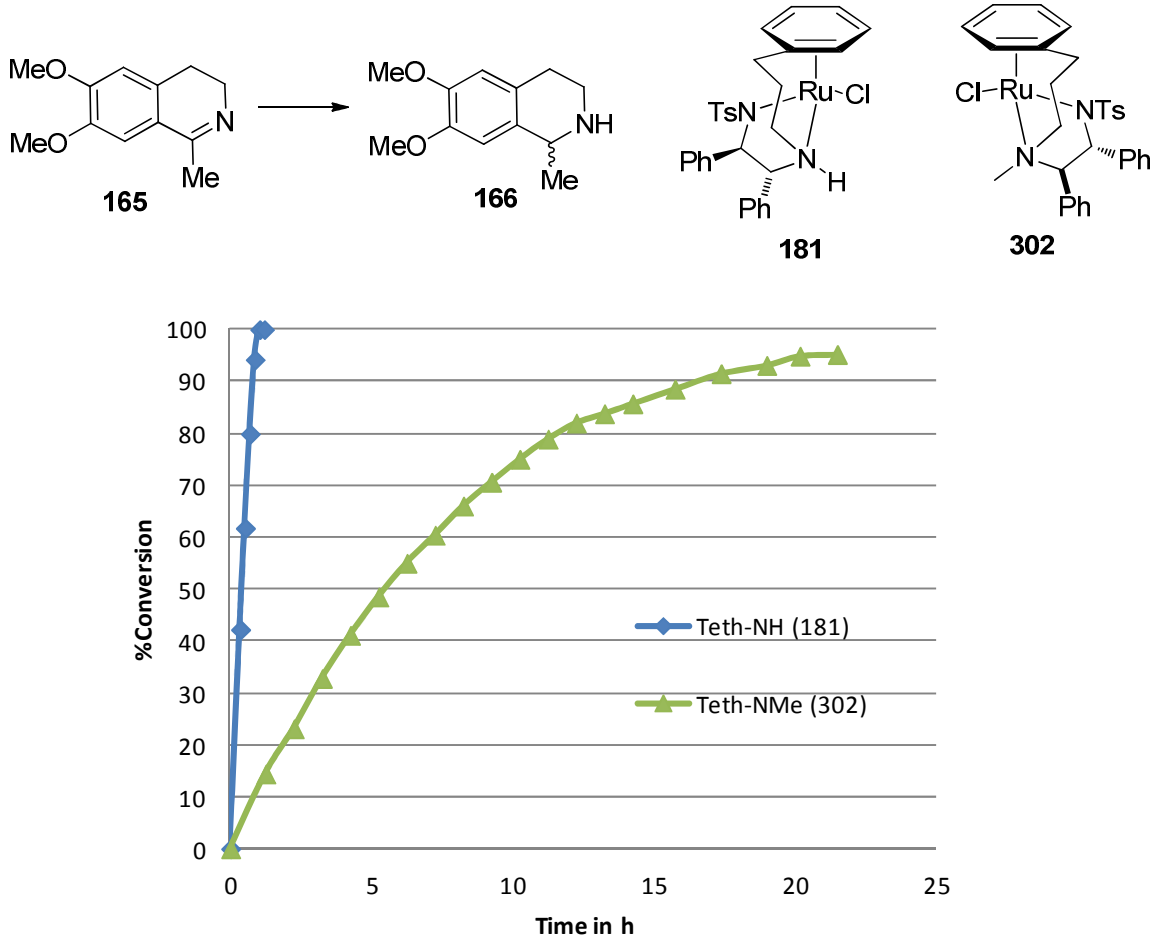


Figure 65: Asymmetric transfer hydrogenation of imine **165** using compounds **181** and **302**. **Conditions:** MeCN, FA/TEA=5:2, [Imine]=0.45 M, 25 ^{o}C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

In this comparative study, ketone reduction was carried out without the use of any additional solvent. To match with the published data, imine reduction was carried out in acetonitrile. During the optimisation of conditions with compound **299**, it was found that the presence of solvent inhibits catalyst activity.

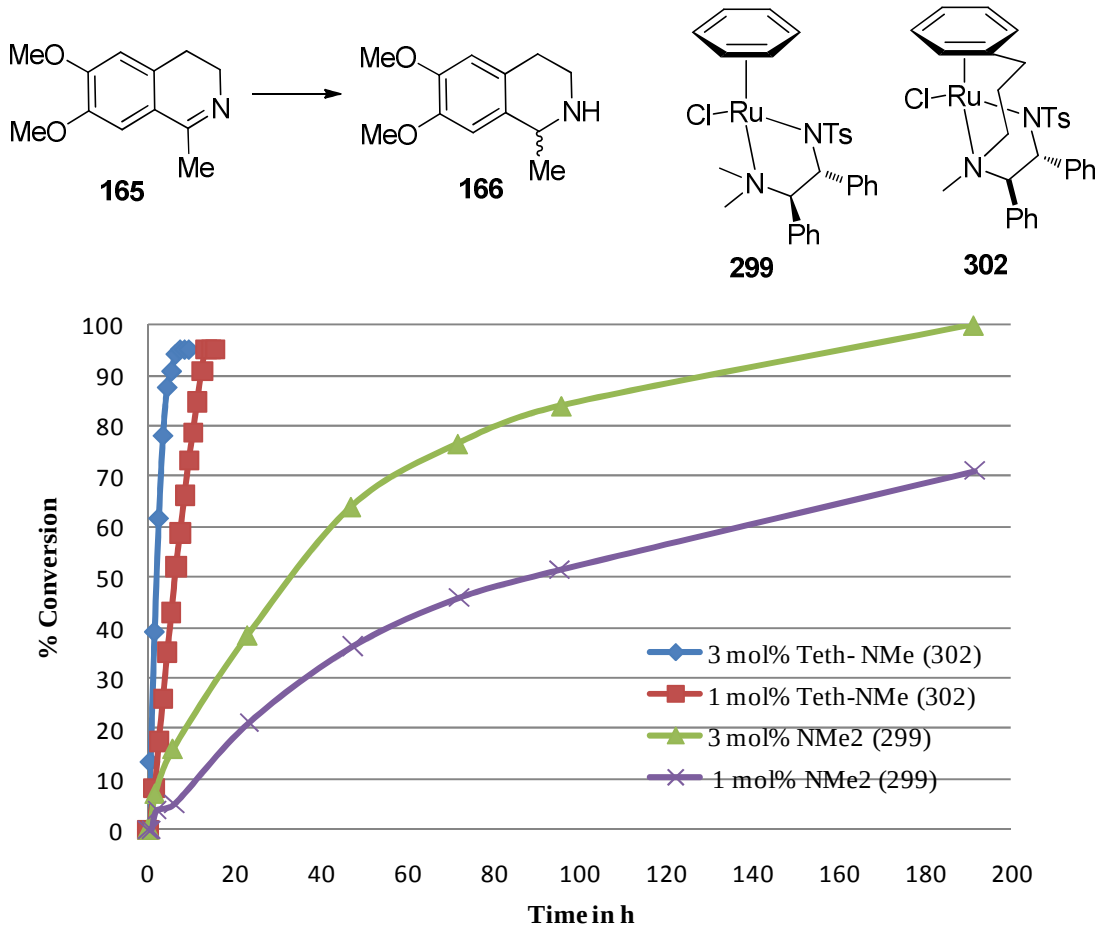


Figure 66: Asymmetric transfer hydrogenation of imine **165** using compounds **299** and **302**. **Conditions:** FA/TEA=5:2, [Imine]=0.50 M, 25 ^{o}C, S/C = 100 and 33. Followed by ^{1}H-NMR (700 MHz).

To overcome the solvent effect, both complexes **299** and **302** were used for imine reduction in FA:TEA without any solvent. At the same time, the reaction was carried out using 1 mol% and 3 mol% catalyst loading (Figure 66). These reactions were carried out in an NMR tube and monitored by ^{1}H-NMR to detect the hydride. Complex **299** exhibited slow reaction with 1 mol% catalyst loading compared to 3 mol% (Figure 66). A similar effect was observed with the complex **302**. However, it can be seen that complex **302** is much faster than complex **299** (Figure 66).

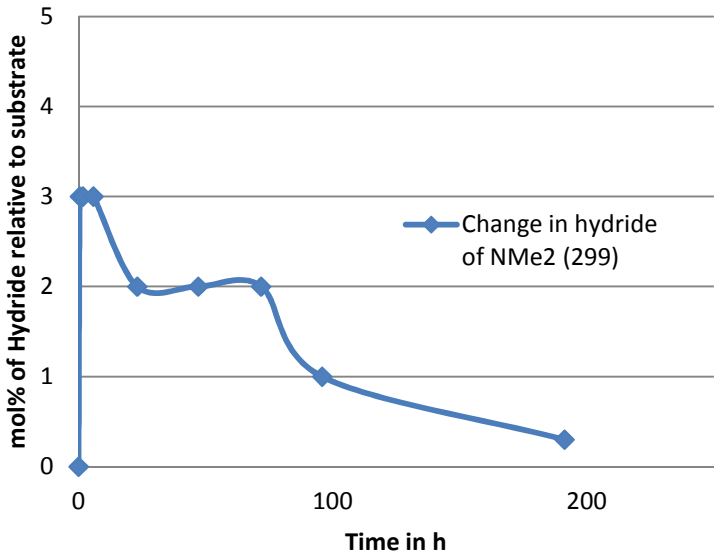


Figure 67: Change in hydride in asymmetric transfer hydrogenation of imine **165** using compound **299. Conditions:** FA/TEA=5:2, [Imine]=0.50 M, 25 ^{o}C, S/C = 33. Followed by ^{1}H-NMR (700 MHz).

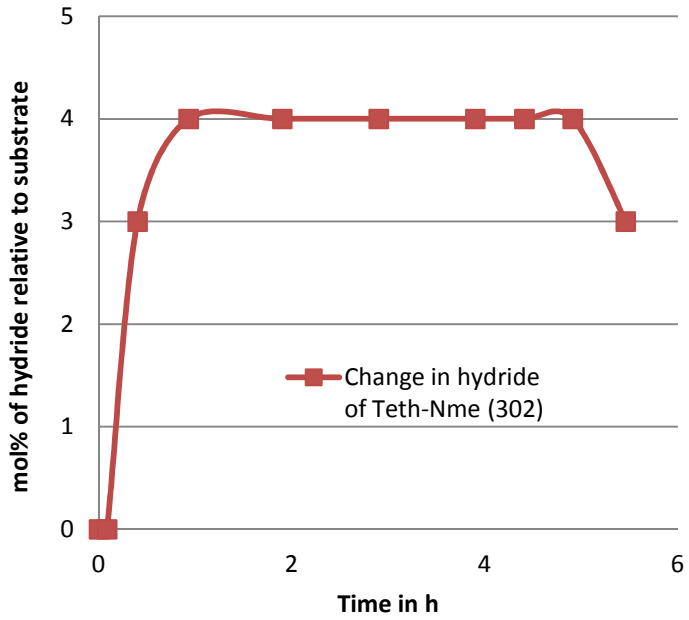


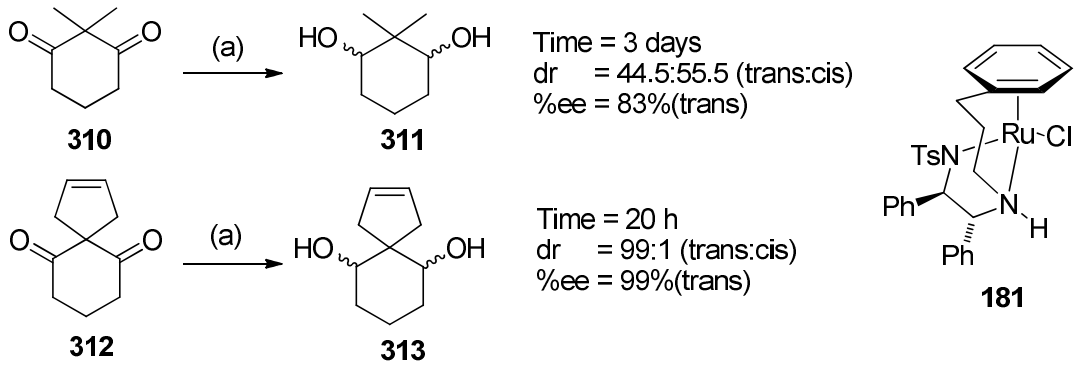
Figure 68: Change in hydride in asymmetric transfer hydrogenation of imine **165** using compound **302. Conditions:** FA/TEA=5:2, [Imine]=0.50 M, 30 ^{o}C, S/C = 33. Followed by ^{1}H-NMR (700 MHz).

In NMR reaction studies, the reactions with 3 mol% of complexes **299** and **302**, the change in the hydride formation was calculated from NMR data. The reaction with 3 mol% loading of compounds **299** and **302** showed a peak for Ru-H at δ-5.4 ppm. The Ru-H peak was integrated and plotted against reaction time (Figures 67 & 68).

The low reactivity of the *N*-alkylated catalysts **299** and **302** relative to the non-alkylated ones could be due to a number of reasons[183,205,207] including (i) catalyst decomposition, (ii) slow formation of the Ru-H species or (iii) slow transfer of the hydride from the Ru-H species to the substrate. The rapid formation of stable Ru-H was observed for the compound **299** and **302**, which would rule out the possibilites of catalyst decomposition and slow hydride formation. Thus, the slow reactivity of compounds **299** and **302** could be the lower rate of transfer of hydride to the imine **165**. Moreover, compounds **299** and **302** were found to be very slow for reduction of ketone, which confirms the concerted mechanism for reduction of ketones under asymmetric transfer hydrogenation conditions. While both compounds **299** and **302** were able to reduced the imine **165** under the asymmetric transfer hydrogenation conditions using FA:TEA, which proves the ionic mechanism for the transfer hydrogenation of imines.

2.4 Asymmetric transfer hydrogenation of hindered ketones

During the investigation of the reduction of 1,3-diketones using Ru-tethered catalysts in the Wills group, project student John-Michel Collinson obtained interesting results for the reduction of 2,2-dimethyl-1,3-cyclohexadione under my supervision for his final year project. Compound **310** was reduced using Ru-3C-tethered catalyst **181** with 2 mol% loading with good selectivity 84% ee and dr = 44.5:55.5 (Scheme 63). The racemic sample of compound **311** was easily prepared by $NaBH_4$ reduction. While compound **312** was reduced using Ru-3C-tethered catalyst **181** with 2 mol% loading in 24 h. The racemic standard could not be prepared using $NaBH_4$ reduction for the enantioselectivity determination of the product using chiral GC/ HPLC. As a result, both (*1R,2R*) and (*1S,2S*) versions of complex **181** were used to prepare both enantiomers of compound **313** separately. With the products in hand, it was revealed that the ee of the major *trans* isomer of **313** was of 99% ee (Scheme 63).



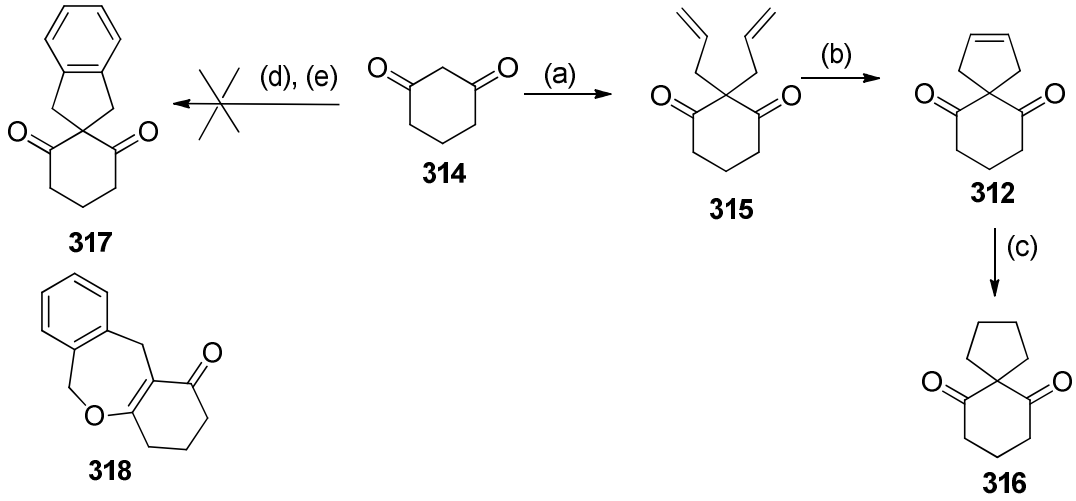
Reagents and Conditions: (a) Catalyst 2 mol%, FA:TEA, 28 °C

Scheme 63: Asymmetric transfer hydrogenation of 1,3-diketones using Ru-3C-tethered complex **181**.

Asymmetric transfer hydrogenation of ketones using η^6-arene-Ru- complexes is well studied in terms of mechanism and origin of enantioselectivity as discussed in

sections 1.4.4 and 1.4.5. High enantioselectivity was obtained for the ketones containing an aryl group, which involves CH-π interaction between the η^6-arene-Ru and the aryl group of the substrate. As a result, the substrates lacking an aryl group were reduced with lower enantioselectivity. Interestingly, compound **312** was reduced with high enantio- and diastereo- selectivity compared to compound **310**. To understand these differences in selectivities between the reduction of compounds **310** and **312**, a series of α,α-disubstituted ketones were synthesised and employed to study the asymmetric transfer hydrogenation using Ru-3C-tethered catalyst **181**.

2.4.1 Synthesis of derivatives of 1,3-cyclohexadione and cyclohexanone



Reagents and Conditions: (a) Allyl bromide, KF on Celite, CH_3CN, 75 °C, 6 h, 33%; (b) Grubb's catalyst 1st Generation, DCM, 22-23 °C, 27 h, 80% (c) Pd/C (10 mol%); H_2 gas, MeOH, 21-22 °C, 18 h, 99%; (d)1,2-(dibromomethyl)benzene, KO^{t}Bu,Toluene, 110 °C, 5 h; (e) 1,2-(dibromomethyl)benzene, K_2CO_3, acetone, 55-56 °C, 50 h, 28%

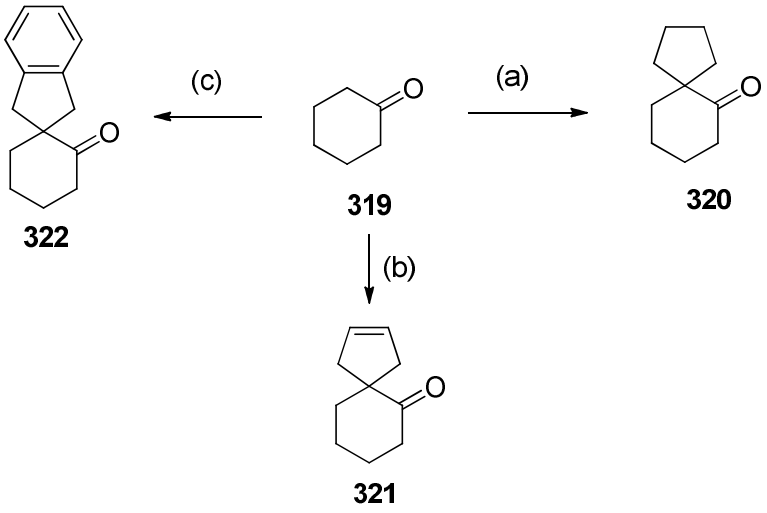
Scheme 64: Synthesis of derivatives of 1,3-cyclohexadione.

The derivatives of 1,3-cyclohexadione were prepared for comparison of the selectivity in asymmetric transfer hydrogenation (Scheme 64).[241] 1,3-Cyclohexadione **314** was converted to the diallyl derivative **315**. The diallyl

compound **315** was subjected to ring closing metathesis using Grubb's 1st generation catalyst to afford compound **312**.

Compound **316** was prepared by Pd/C hydrogenation of compound **312**. 1,3-cylcohexadione **314** was reacted under two different condition with 1,2-(dibromomethyl)benzene in an attempt to prepare compound **317**. None of the conditions afforded the required product and one of the side products was identified as compound **318** (Scheme 64).

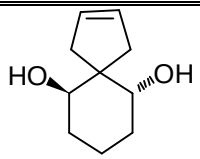
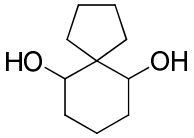
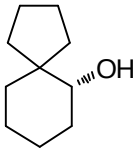
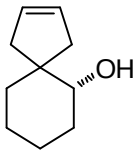
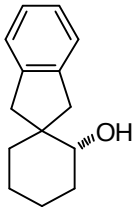
To compare the selectivity between 1,3-diketone and mono ketone reductions, some derivatives of cyclohexanone **319** were synthesised (Scheme 65).[242-244] Cyclohexanone **319** was successfully reacted with 1,4-dibromobutane to give compound **320** and with 1,4-dichloro-2-butene to afford compound **321**. Cyclohexanone **319** was reacted with 1,2-(dibromomethyl)benzene to give compound **322**.



Reagents and Conditions: (a)1,4-dibromobutane, KO^{t}Bu,Toluene, 110 ^{o}C, 5 h, 21%; (b) 1,4-dichloro-2-butene, Na, *tert*-amyl alcohol, Toluene, 110 ^{o}C, 48 h, 16%; (c) 1,2-(dibromomethyl)benzene, KO^{t}Bu, ^{t}BuOH, 26-27 ^{o}C, 24 h, 45%.

Scheme 65: Synthesis of derivatives of cyclohexanone.

Table 39: Asymmetric transfer hydrogenation of compounds **312**, **316**, **320**, **321** and **322** using Ru-3C-tethered catalyst **181**.

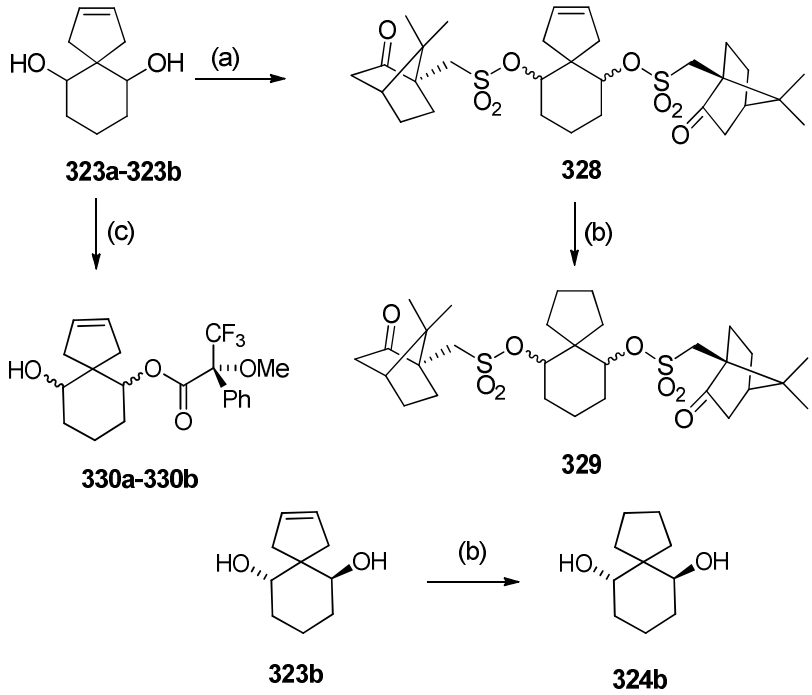
Compd	Catalyst mol%	Temp	Time[a]	%ee[b]	dr trans:cis[d]	Product
312	2 mol%	28 °C	21 h	99%	99:1	 **323a**
316	2 mol %	45 °C	46 h	99%	35:65	 *trans* **324a** *cis* **324c**
318	1 mol%	30 °C + 60 °C	1 day 1 day	NR	-	-
320	1 mol%	28 °C	22 h	71%	-	 **325a**
321	1 mol%	28 °C	18 h	96%	-	 **326a**
322	1 mol%	28 °C	22 h	93%[c]	-	 **327a**

[a] Completion of reaction was checked by ^{1}H-NMR, [b]The enantiomeric excess is calculated from chiral GC after acetate derivative of reduced product, [c] The enantiomeric excess is calculated from chiral HPLC, [d]The dr is calculated from ^{1}H-NMR of crude product. NR = No reaction

Compounds **312**, **316**, **320**, **321** and **322** were used in asymmetric transfer hydrogenation using Ru-3C-tethered catalyst **181** (Table 39). Compound **312** was reduced at 28 ^{o}C in 21 h with high enantioselectivity (99% ee) and diastereoselectivity (*trans*:*cis* 99:1) using 2 mol % of **181**(Table 39). Asymmetric transfer hydrogenation of compound **316** was required a higher temp (45 ^{o}C) for 36 h to give complete conversion. The reduction of compound **316** was found to have low diastereoselectivity with a *trans*:*cis* ratio 35:65, and the *trans* diastereomer was of 99% ee (Table 39). These contradictory results between enantio- and diastereo-selectivities can be explained by undiastereoselective second reduction controlled by the mono reduced product itself rather than catalyst. Compound **318** did not give any reduction at 30 ^{o}C for 1 day followed by heating to 60 ^{o}C for 1 more day using Ru-3C-tethered catalyst **181** (Table 39).

Compound **320** with mono ketone and a saturated ring, was reduced with a low enantioselectivity of 71% ee for transfer hydrogenation using Ru-3C-tethered catalyst **181** (Table 39). Interestingly, compound **321** was reduced with high enantioselectivity (96% ee) in 18 h at 28 ^{o}C using Ru-3C-tethered catalyst **181** (Table 39). Similarly, compound **322** with an aromatic substituent was also reduced with high enantioselectivity (93% ee) (Table 39). The differences in selectivity of compounds **320**, **321** and **322** may be due to the presence of an unsaturation or an aromatic group. The alcohol compounds obtained by asymmetric transfer hydrogenation of compounds **312**, **316**, **320**, **321** and **322** (Table 39) were all novel. It was required to first establish the configuration of these novel alcohols to understand the difference in enantioselectivity between them during the asymmetric transfer hydrogenation using complex **181**.

The configuration of a novel alcohol can be obtained by two different methods (i) reaction of the enantiopure compound with known chiral compounds followed by X-ray crystallography and (ii) Mosher's method[245].



Reagents and Conditions: (a) (1*S*)-(+)-10-Camphorsulfonyl chloride, TEA, DMAP, DCM, 20-21 °C, 24 h, 84%; (b) Pd/C (10 mol%); H_2 gas, MeOH, 21-22 °C, 18 h, 89-99%; (c) (*S*)-(+)-MTPA-Cl, TEA, DMAP, DCM, 20-21 °C, 17 h, 43%

Scheme 66: Identification of configuration of compounds **323a** and **324b.**

Compound **323a** was reacted with (1*S*)-(+)-camphorsulfonyl chloride to give the ester derivative **328** (Scheme 66), however attempts to crystallise this in different solvents resulted in formation of an oily compound. Compound **328** was subjected to Pd/C hydrogenation to reduce the double bond but the resulting compound **329** was again found to be an oil (Scheme 66). As compounds **328** and **329** were both oils, Mosher's method was used to find the configuration of **323a**.[245] The alcohols **323a** and **323b** were obtained using the (1*R*,2*R*) and (1*S*,2*S*) complexes of **181** and were

reacted with (*S*)-(+)-MTPA-Cl to give two diastereomers **330a** and **330b** (Scheme 66).

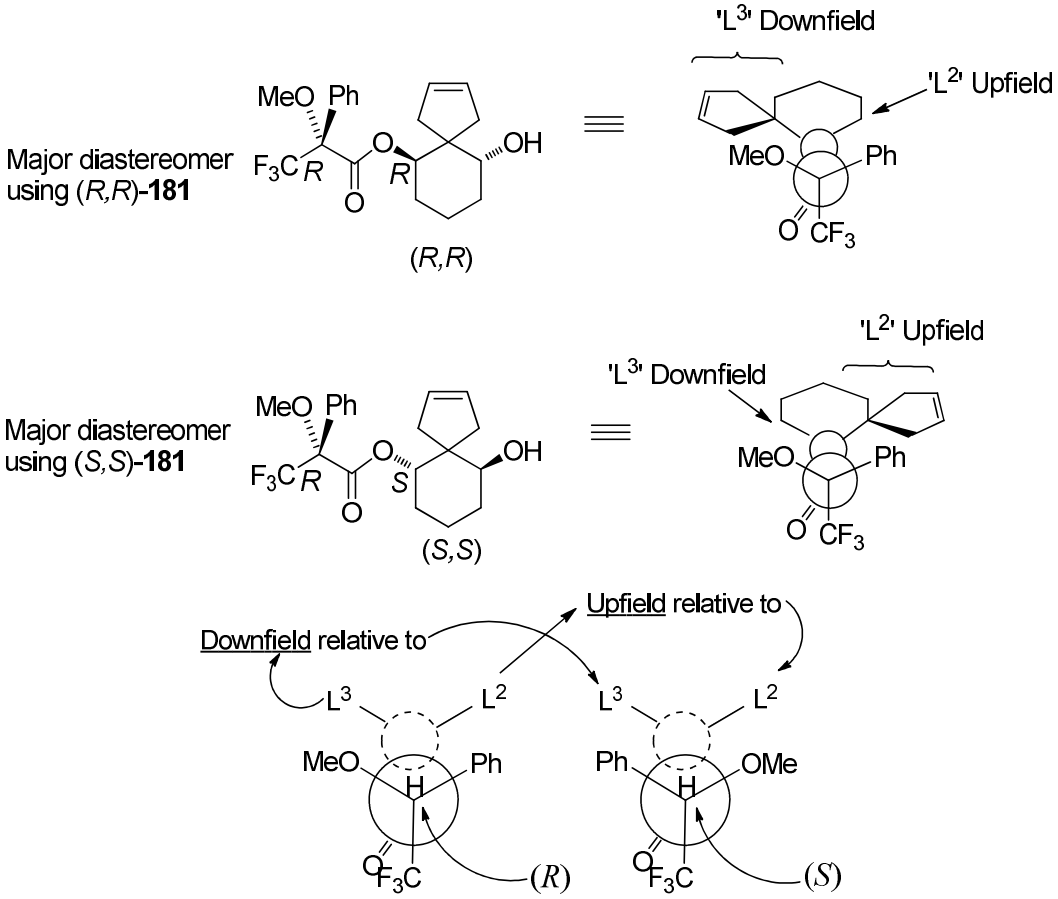
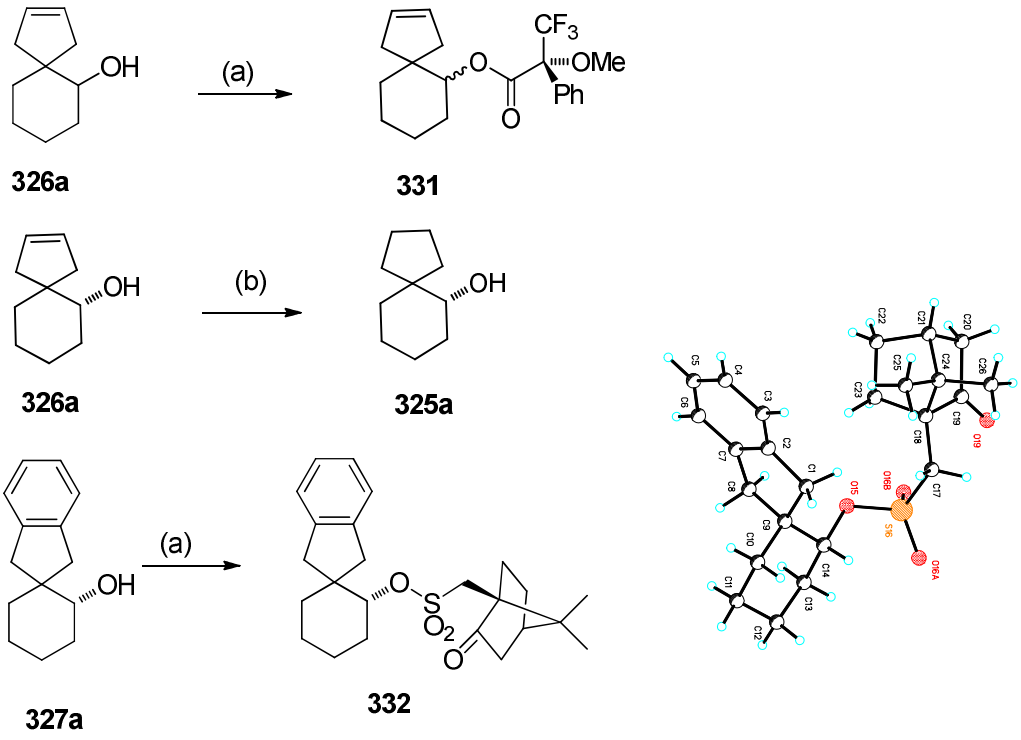


Figure 69: Mosher's method for absolute configuration.[245]

The ^{1}H-NMR spectra of both Mosher's esters **330a** and **330b** were analysed for relative changes in peaks for substituents next to the alcohol group (Figure 69). From the relative position of the group in ^{1}H-NMR for both diastereomers, the configuration of starting alcohol can be obtained using the model shown in Figure 69. Compound **312** was reduced in *R,R* configuration using (1*R*,2*R*) complex **181** (More details in Appendix 5.2 and ^{1}H-NMR spectra in Appendix 5.2.1). At the same time, compound **323b** obtained using (1*S*,2*S*) complex **181** was reduced to compound **324b**, which is the opposite isomer to that obtained using (1*R*,2*R*) catalyst

181 (Scheme 66). Thus, compounds **312** and **316** were reduced in the similar way by (1*R*,2*R*) complex **181**.



Reagents and Conditions: (c) (*S*)-(+)-MTPA-Cl, TEA, DMAP, DCM, 20-21 ^{o}C, 17 h, 49%; (b) Pd/C (10 mol%); H_2 gas, MeOH, 21-22 ^{o}C, 18 h, 88%; (c) (1*S*)-(+)-10-Camphorsulfonyl chloride, TEA, DMAP, DCM, 20-21 ^{o}C, 24 h, 48%;

Scheme 67: Identification configuration of compounds **326a**, **325a** and **327a**.

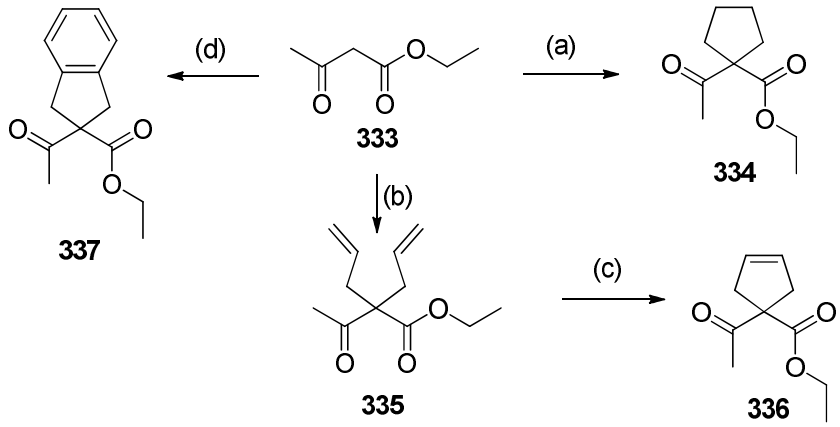
The alcohols **326a** and **326b** obtained by using the (1*R*,2*R*) and (1*S*,2*S*) complexes of **181** were reacted with (*S*)-(+)-MTPA-Cl to give two diastereomers **331a** and **331b** (Scheme 67). The ^{1}H-NMR spectra of both Mosher's esters **331a** and **331b** were analysed for relative changes in the peaks for substituents next to the alcohol group. From the relative position of the group in ^{1}H-NMR for both diastereomers, compound **321** was reduced in *R* configuration using (1*R*,2*R*) complex **181**(More details in Appendix 5.2). At the same time, compound **326a** obtained using (1*R*,2*R*) complex **181** was reduced to compound **325a** which is the same enantiomer to that obtained using (1*R*,2*R*) catalyst **181** (Scheme 67). Compound **327a** was reacted (1*S*)-

(+)-camphorsulfonyl chloride to give sulfonyl ester **332**, which was recrystallised to give good quality crystals for X-ray crystallography (Scheme 67). The X-ray structure of **332** confirmed its reduction in *R* configuration, similar to compounds **320** and **321**.

Compounds **312**, **316**, **320**, **321** and **322** were reduced to their alcohols with *R* configurations at the chiral centre using (1*R*,2*R*) complex **181**. Compound **181** gave complete conversion in 18-22h with enantioselectivities in the range of 93-99% for asymmetric transfer hydrogenation of compounds **312**, **321** and **322** (Table 39). At the same time, asymmetric transfer hydrogenation of compounds **316** and **320** were found to be slower and less selective (Table 39). These differences in efficiency and selectivity may be due to the presence of unsaturation or aryl group present in compounds **312**, **321** and **322**, which can give some weak interaction between η^6-arene-Ru of compound **181** and unsaturation or aryl group of substrate.

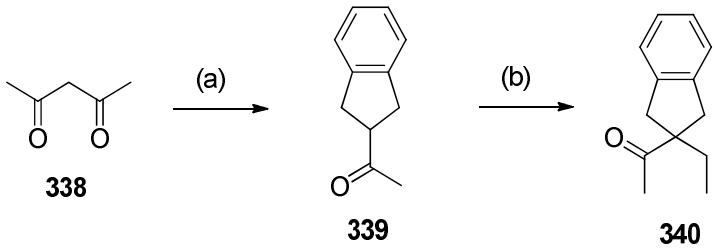
2.4.2 Synthesis of derivatives of ethyl acetoacetate and acetylacetone

In order to improve the substrate scope and complete a comparative study of the effect of unsaturation or an aryl group in the control of enantioselectivity, different derivatives of ethyl acetoacetate were prepared.[246-248] In these derivatives, the ketone group is not part of the ring. Compounds **334** and **337** were prepared by the reaction of EAA **333** with 1,4-dibromobutane and 1,2-(dibromomethyl)benzene respectively as shown in Scheme 68. Compound **336** was prepared by diallyl derivative **334** of EAA followed by ring closing metathesis using Grubb's 1st generation catalyst (Scheme 68). Compound **340** was prepared following a reported procedure.[249] Acetylacetone **338** was reacted with 1,2-(dibromomethyl)benzene to give compound **339**, which was alkylated using ethyl iodide to afford compound **340** (Scheme 69).



Reagents and Conditions: (a)1,4-dibromobutane, KO^{t}Bu, DMSO, 21-22 ^oC, 3 days, 70%; (b) allyl bromide, K_2CO_3, DMF, 80 ^oC, 20 h, 93%; (c) Grubb's catalyst 1st Generation, DCM, 22-23 ^oC, 24 h, 92%; (d) 1,2-(dibromomethyl)benzene, TBAB,48% NaOH, Toluene, 22 ^oC, 3.5 h, 70%;

Scheme 68: Synthesis of derivatives of ethyl acetoacetate.

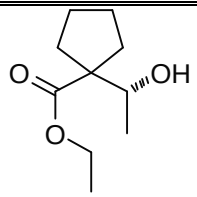
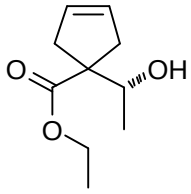
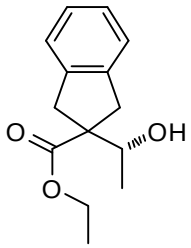
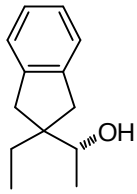


Reagents and Conditions: (a) 1,2-(dibromomethyl)benzene, TBAB, 48% NaOH, Toluene, 80-85 ^oC, 5 h, 41%; (b) KO^{t}Bu, THF, ethyl iodide, -20 ^oC, 3 h, 23-24 ^oC, 1.5 h, 55%.

Scheme 69: Synthesis of 1-(2-ethyl-2,3-dihydro-1H-inden-2-yl)ethanone.

Asymmetric transfer hydrogenation of compound **334** was found to be slow and took 47 h to give complete conversion using the (1*R*,2*R*) complex **181** (Table 40). At the same time, $NaBH_4$ reduction did not work to give a racemic sample. The reduction of compound **334** was also carried out using the (1*S*,2*S*) complex **181** to get the opposite isomer. Compound **334** was reduced with very low enantioselectivity (61% ee, Table 40). On the other hand, compounds **336** and **337** were reduced with high enantioselectivity with 92% and 90% ee respectively (Table 40).

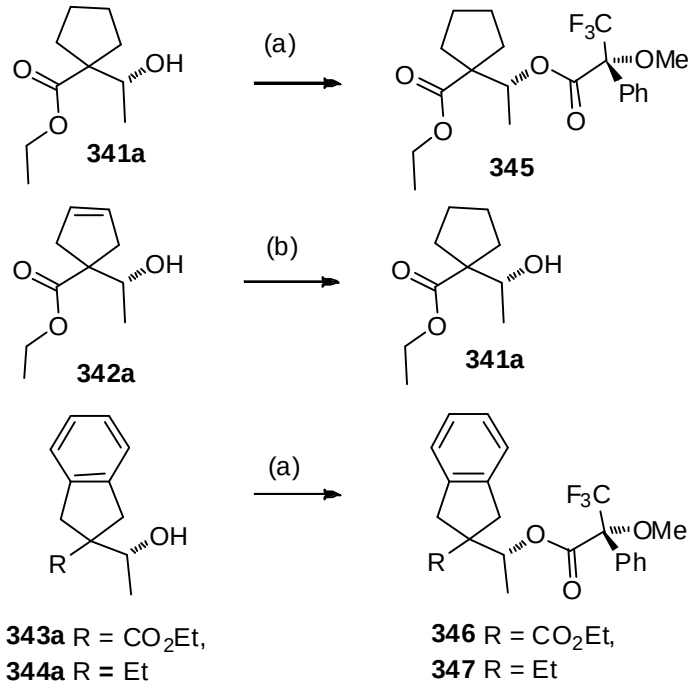
Table 40: Asymmetric transfer hydrogenation of compounds **334**, **336**, **337** and **340** using Ru-3C-tethered catalyst **181**.

Compound	Catalyst mol%	Temp	Time[a]	%ee	Product
334	1 mol%	30 °C	47h	61%[b]	 **341 a**
336	1 mol%	28 °C	30 h	92%[b]	 **342 a**
337	1 mol%	28 °C	17 h	90%[c]	 **343 a**
340	1 mol%	28 °C	24 h	73%[c]	 **344 a**

[a] Completion of reaction was checked by ^{1}H-NMR, [b] The enantiomeric excess is calculated from chiral GC after acetate derivative of reduced product, [c] The enantiomeric excess is calculated from chiral HPLC.

In contrast, compound **340** was reduced with moderate enantioselectivity with 73% ee (Table 40). Asymmetric transfer hydrogenation of compound **340** can easily be

compared with compound **337**; the selectivity differences between both compounds may be due to the ester group, which may give rise to an extra interaction with Ru-catalyst and result in high enantioselectivity. The alcohols obtained by reductions of compounds **334**, **336**, **337** and **340** were all novel (Table 40). The Mosher's method was used to identify the configuration of these alcohols (Scheme 70).



Reagents and Conditions: (a) (*S*)-(+)-MTPA-Cl, TEA, DMAP, DCM, 20-21 ^{o}C, 17 h, 46-66%; (b) Pd/C (10 mol%); H_2 gas, MeOH, 21-22 ^{o}C, 18 h, 91%.

Scheme 70: Identification of configuration of compounds **341a**, **342a**, **343a** and **344a.**

Mosher's ester derivatives were prepared for compounds **341a** and **341b** (using (1*R*,2*R*) and (1*S*,2*S*) complexes of **181** respectively) and compared by ^{1}H-NMR for respective shifts in the peak of substitution next to the alcohol(More details in Appendix 5.2 and ^{1}H-NMR spectra in Appendix 5.2.2).[245] Compound **336** was reduced in *R* configuration using (1*R*,2*R*) complex **181**. Compound **342a** (obtained using (1*R*,2*R*) catalyst **181**) was reduced using Pd/C to give compound **341a**, which

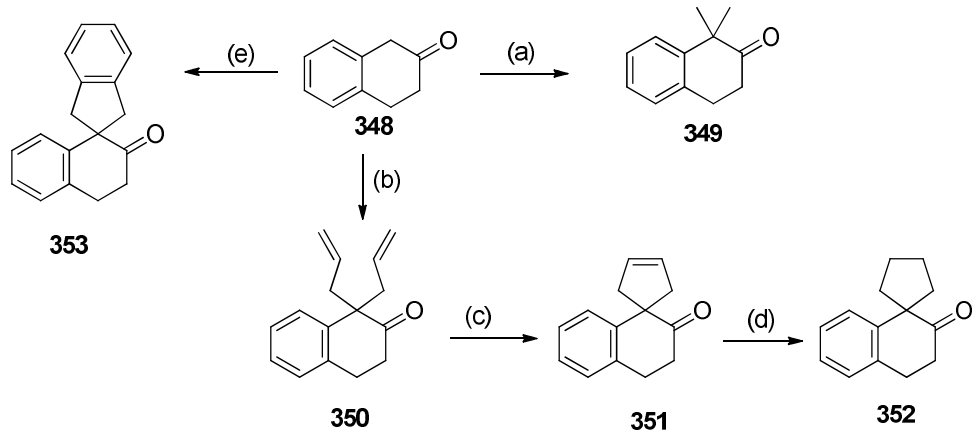
is same enantiomer as obtained by direct reduction of compound **334** using (1*R*,2*R*) catalyst **181** (Scheme 70). Thus, both compounds **334** and **336** were reduced in a similar way using (1*R*,2*R*) complex **181**. Compounds **337** and **340** were also reduced in *R* configuration using (1*R*,2*R*) complex **181**, confirmed by Mosher's ester analysis (More details in Appendix 5.2 and ^{1}H-NMR spectra in Appendix 5.2.3 & 5.2.4).

Asymmetric transfer hydrogenation using (1*R*,2*R*) Ru complex **181**, was highly enantioselective for compound **337** containing an aryl substituent and compound **336** with an unsaturated cyclic group compared to compound **334**. Thus, unsaturated cyclic ring or aryl substituents of the substrates can interact with catalyst to orient ketone group to give enantioselective reduction. (1*R*,2*R*) Ru complex **181** gave complete conversion with low enantioselectivity for asymmetric transfer hydrogenation of compound **340**, even though there was an aromatic ring in the substrate (Table 40). This low enantioselectivity may be due to the hindered ethyl group near to the carbonyl group. While in compounds **334**, **336** and **337**, the ester group may have some interaction with the (1*R*,2*R*) Ru complex **181**, but it is hard to predict.

2.4.3 Synthesis of derivatives of β-tetralone and α-tetralone

As discussed in sections 2.4.1 and 2.4.2, the reduction of ketone derivatives containing unsaturated cyclic rings or aryl substituents was more enantioselective compared to compounds lacking such groups. The mechanism for acetophenone is well studied and involves a CH-π interaction between arene ring of catalyst and the aryl group of the substrate as discussed in section 1.4.5. To identify the dominating interaction, the reductions of ketones having both an aryl substituent for CH-π

interaction (such as acetophenone) and a cyclic ring with unsaturation or an aryl group were selected.



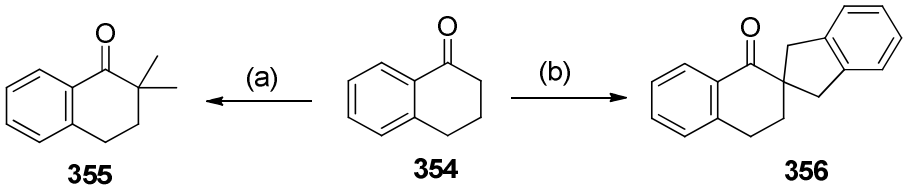
Reagents and Conditions: (a) MeI, TBAS, 48% KOH, THF, 22-23 °C, 30 min, 86%; (b) allyl bromide, K_2CO_3, DMF, 80°C, 4 h, 64%; (c) Grubb's catalyst 1st Generation, DCM, 22-23 °C, 24 h, 84%; (d) Pd/C (10 mol%), H_2 gas, EtOAc, 21-22 °C, 24 h, 70%; (e) 1,2-(dibromomethyl)benzene, TBAB, 48% NaOH, Toluene, 22-23 °C, 4 h, 70%.

Scheme 71: Synthesis of derivatives of β-tetralone.

Derivatives of β-tetralone and α-tetralone were synthesised as described in Schemes 71 and 72.[250-25] β-Tetralone **348** was reacted with iodomethane to give compound **349**. Compound **351** was prepared by formation of the diallyl derivative **350** of β-tetralone **348** followed by ring closing metathesis using Grubb's 1st generation catalyst. Compound **351** was hydrogenated using Pd/C to give compound **352**. Compound **353** was prepared by reaction of β-tetralone with 1,2-(dibromomethyl)benzene. Similarly, compounds **355** and **356** were prepared by reaction of α-tetralone **354** with iodomethane and 1,2-(dibromomethyl)benzene respectively.

β-Tetralone **348** was reduced with good enantioselectivity of 88% ee under asymmetric transfer hydrogenation conditions using (1*R*,2*R*) Ru complex **181** (Table 41). Compound **349** was reduced with high enantioselectivity (94% ee) and at a faster rate with complete conversion in 9 h at 28 °C (Table 41). Compounds **351** and

352 were also reduced in 18-20 h with 99% ee using (1*R*,2*R*) Ru complex **181** (Table 41). Compound **353** was reduced in >99% ee at 28 ^{o}C in 24 h using (1*R*,2*R*) Ru complex **181** (Table 41). High enantioselectivity for transfer hydrogenation of compounds **349** and **351**-**353** was obtained compared to β-tetralone **348**.



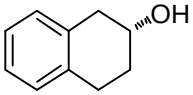
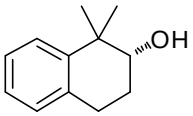
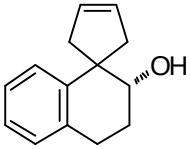
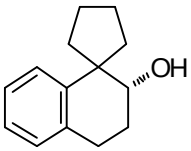
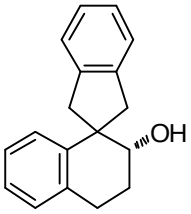
Reagents and Conditions: (a) MeI, NaH, THF, 40 ^{o}C, 45 min, 65%;
(b) 1,2-(dibromomethyl)benzene, KO^{t}Bu, ^{t}BuOH, 26-27 ^{o}C, 18 h, 58%.

Scheme 72: Synthesis of derivatives of α-tetralone.

β-Tetralone **348** was reduced with good enantioselectivity of 88% ee under asymmetric transfer hydrogenation conditions using (1*R*,2*R*) Ru complex **181** (Table 41). Compound **349** was reduced with high enantioselectivity (94% ee) and at a faster rate with complete conversion in 9 h at 28 ^{o}C (Table 41). Compounds **351** and **352** were also reduced in 18-20 h with 99% ee using (1*R*,2*R*) Ru complex **181** (Table 41). Compound **353** was reduced in >99% ee at 28 ^{o}C in 24 h using (1*R*,2*R*) Ru complex **181** (Table 41). High enantioselectivity for transfer hydrogenation of compounds **349** and **351**-**353** was obtained compared to β-tetralone **348**.

On the other hand, the derivatives of α-tetralone compound **355** and **356** required higher temperatures to give complete conversion (Table 42). This may be due to the bulkiness around the ketone group. The reduction of both compounds **355** and **356** was highly selective 98-99% ee using (1*R*,2*R*) Ru complex **181** at 45 ^{o}C over a period of 48 h and 24 h respectively (Table 42).

Table 41: Asymmetric transfer hydrogenation of compounds **348**-**349** and **351**-**353** using Ru-3C-tethered catalyst **181**.

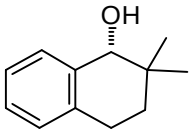
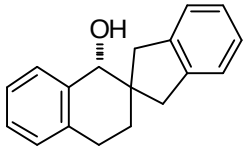
Compound	Catalyst mol%	Temp	Time[a]	%ee	Compound
348	1 mol%	28 °C	30 h	88%[b]	 **357a**
349	1 mol%	28 °C	9 h	94%[b]	 **358a**
351	1 mol%	28 °C	20 h	99%[c]	 **359a**
352	1 mol%	28 °C	18 h	99%[c]	 **360a**
353	1 mol%	30 °C	24 h	99%[c]	 **361a**

[a] Completion of reaction was checked by ^{1}H-NMR, [b] The enantiomeric excess is calculated from chiral GC after acetate derivative of reduced product, [c] The enantiomeric excess is calculated from chiral HPLC.

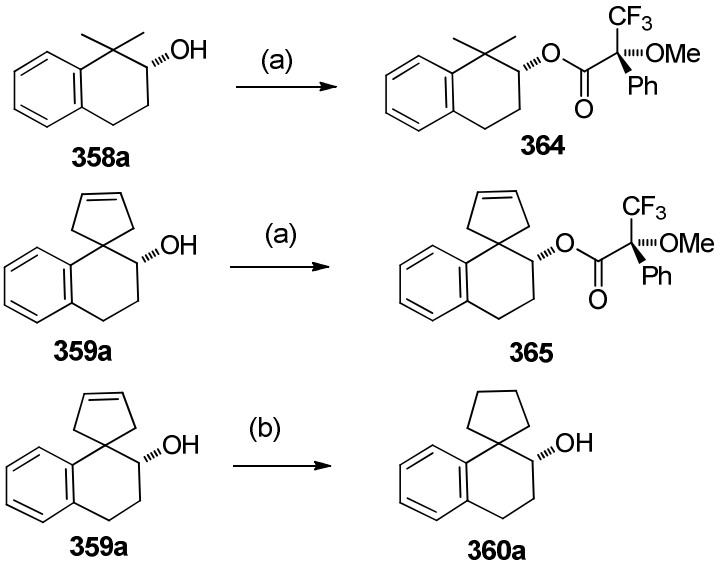
The alcohol derivatives obtained by reduction of compounds **349**, **351**-**353** and **356** were novel (Tables 41 & 42). It is necessary to identify the configurations of these alcohols in order to understand the orientation of molecule in catalytic cycle. The configuration of compounds **358a** and **359a** were obtained as *R* configurations by using Mosher's method(More details in Appendix 5.2 and ^{1}H-NMR spectra in

Appendix 5.2.5 & 5.2.6).[245] Compound **359a** was reduced by Pd/C to give compound **360a**, the same as that obtained by direct asymmetric transfer hydrogenation of compound **352** by using (1*R*,2*R*) complex **181**.

Table 42: Asymmetric transfer hydrogenation of compounds **355**-**356** using Ru-3C-tethered catalyst **181**.

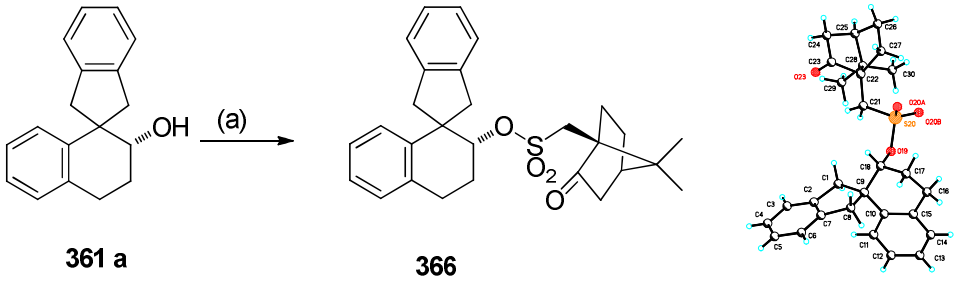
Compound	Catalyst mol%	Temp	Time[a]	%ee	Compound
355	1 mol%	45 °C	49 h	98%[b]	 **362a**
356	1 mol%	45 °C	24 h	99%[c]	 **363a**

[a] Completion of reaction was checked by ^{1}H-NMR, [b] The enantiomeric excess is calculated from chiral GC after acetate derivative of reduced product, [c] The enantiomeric excess is calculated from chiral HPLC.



Reagents and Conditions: (a) (*S*)-(+)-MTPA-Cl, TEA, DMAP, DCM, 20-21 °C, 17 h, 38-53%; (b) Pd/C (10 mol%); H_2 gas, MeOH, 21-22 °C, 18 h, 99%.

Scheme 73: Identification of configuration of compounds **358a**, **359a** and **360a.**



361 a **366**

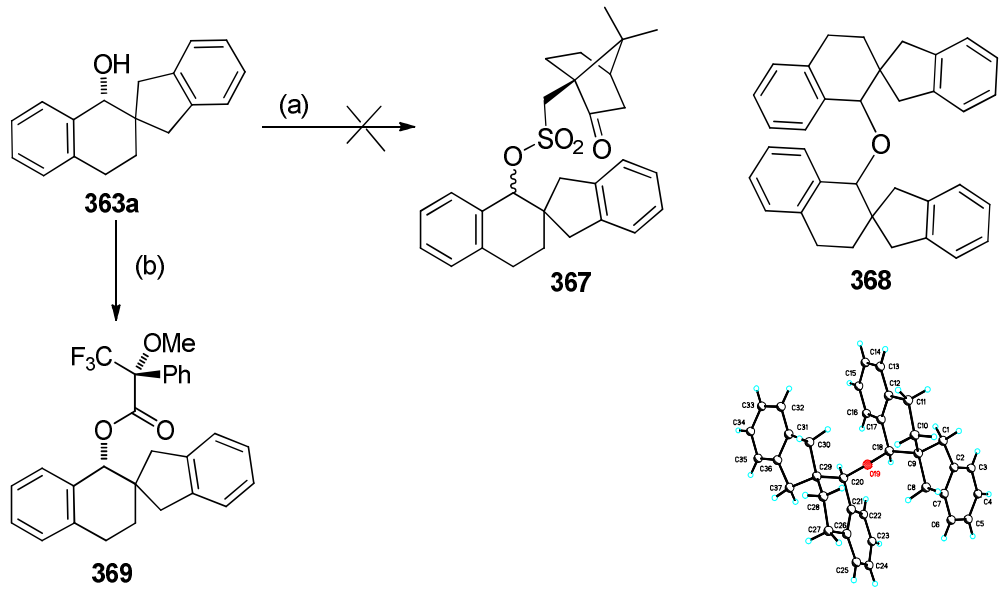
Reagents and Conditions: (a) (1*S*)-(+)-10-Camphorsulfonyl chloride, TEA, DMAP, DCM, 20-21 °C, 24 h, 64%

Scheme 74: Identification of configuration of compound **310a.**

Compound **361a** was reacted with (1S)-(+)-camphorsulfonyl chloride to give the ester derivative **366**, which was recrystallised to give a crystal for X-ray crystallography (Scheme 74). The X-ray structure of compound **366** confirmed that compound **353** was reduced in a similar way to give the *R* configuration as compounds **349**, **351** and **352**. During an attempt to form the camphorsulfonyl ester of compound **363a**, the ether linked product **368** was formed as a *meso* ether instead of the required compound **367** (Scheme 75). The structure of **368** was also confirmed by X-ray structure analysis (Scheme 75). Mosher's method was used to identify the absolute configuration of compound **363a** as "*R* configuration" by ^{1}H-NMR analysis of resulting Mosher's ester (More details in Appendix 5.2 and ^{1}H-NMR spectra in Appendix 5.2.7).[245]

(1*R*,2*R*) complex **181** gave complete conversion and high enantioselectivities for asymmetric transfer hydrogenation of compounds **348-349** and **351-353** with *R* configuration. These results show that interaction between η^6-arene-Ru and aryl group originally coming from the tetralone is much stronger compared to the interaction between η^6-arene-Ru and the cyclic ring with unsaturation or aryl group. Thus, enantioselectivity was controlled by stronger interactions to give the *R*

configuration in all alcohol products. A similar trend of interactions was also observed in asymmetric transfer hydrogenation of compound **355** using (1*R*,2*R*) complex **181**.



Reagents and Conditions: (a) (1*S*)-(+)-10-Camphorsulfonyl chloride, TEA, DMAP, DCM, 20-21 ^{o}C, 24 h, 58%; (b) (*S*)-(+)-MTPA-Cl, TEA, DMAP, DCM, 20-21 ^{o}C, 17 h, 35%

Scheme 75: Identification of configuration of compound **316a.**

2.4.4 Asymmetric transfer hydrogenation of selected compounds using Noyori's catalyst 153

The bridging chain of (1*R*,2*R*) complex **181** may give rise to some interaction during the catalytic cycle with the group placed on α position of ketone. To overcome this possibilities, selected compounds were reduced using (1*R*,2*R*) Noyori's catalyst **153**. For almost all tested compounds, (1*R*,2*R*) Noyori's catalyst **153** was found to be much slower compared to the (1*R*,2*R*) Ru-3C-tethered catalyst **181** (Table 43). At the same time, the enantioselectivities were unaffected in all the compounds and were almost similar to (1*R*,2*R*) Ru-3C-tethered catalyst **181**. Thus, the bridging chain of (1*R*,2*R*) complex **181** is not interacting with the substrates

during the catalytic cycle. Interestingly, (1*R*,2*R*) Noyori's catalyst **153** was not able to reduce compound **356** even after a long reaction time at high temperature (Table 43). Thus, the asymmetric transfer hydrogenations of α,α-disubstituted ketones using Ru-3C-tethered catalyst **181** is quite promising with the weak interaction of an unsaturation or an aromatic group in substitution at the α-position of the ketone with catalysts.

Table 43: Asymmetric transfer hydrogenation of selected compounds using (1*R*,2*R*) Noyori's catalyst **153**.

Compd	Catalyst mol%	Temp	Time[a]	%ee	Compound
312	4 mol%	30 ^{o}C	7 days[b]	92% (*R*)[c]	**323a**
322	1 mol%	28 ^{o}C	48h	94% (*R*)[d]	**327a**
337	1 mol%	28 ^{o}C + 60 ^{o}C	24 h + 5h	91% (*R*)[d]	**343a**
353	1 mol%	28 ^{o}C	24 h	99% (*R*)[d]	**361a**
356	1 mol%	45 ^{o}C	48 h	NR[e]	-

[a] Completion of reaction was checked by ^{1}H-NMR, [b] 15% of mono reduced product was present by ^{1}H-NMR, [c]The enantiomeric excess is calculated from chiral GC after acetate derivative of reduced product, [d] The enantiomeric excess is calculated from chiral HPLC, [e] NR= No reaction.

The high enantioselectivity obtained for asymmetric transfer hydrogenation of compounds **312**, **321**, **322**, **336** and **337** using (1*R*,2*R*) complex **181**, can be explained by the possible CH-π interaction between the (1*R*,2*R*) complex **181** and compounds **321**, **322** and **337** as shown in Figures 70a, 70b and 70c respectively. Moreover, the carbonyl group (as ketone or ester) present in compounds **312**, **336** and **337** may give rise to a possible interaction between the carbonyl oxygen and the -CH of the η^{6}-arene-Ru complex as shown in Figures 70a and 70c.

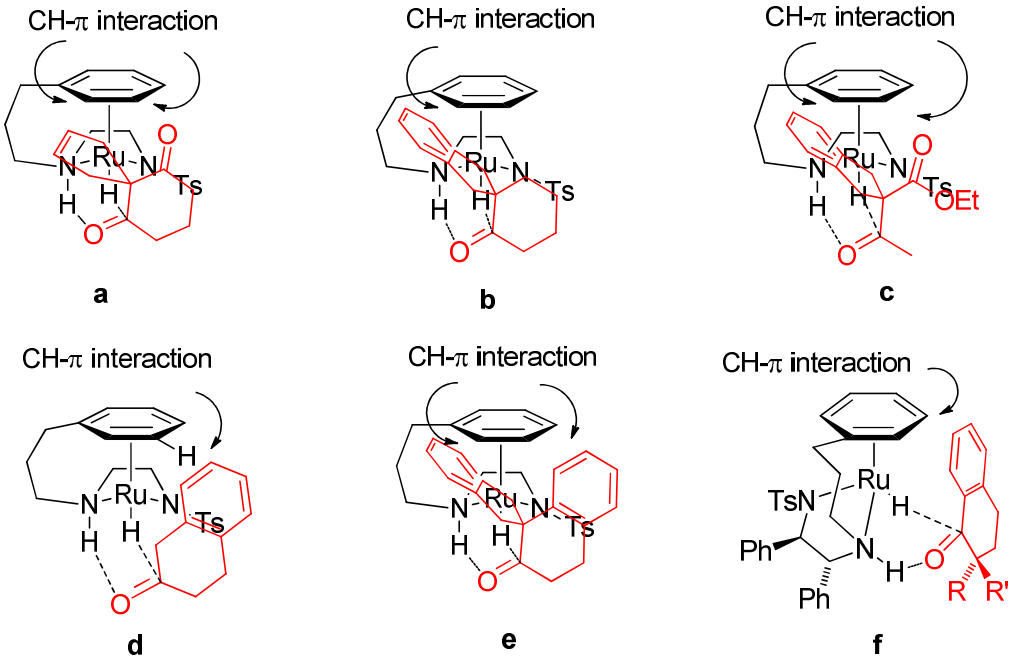


Figure 70: Possible stabilizing interactions in transition states of reduction of α,α-disubstituted ketones.

The β-tetralone is reduced with good enantioselectivity of 88% ee using (1*R*,2*R*) complex **181** that can be explained by the already established CH-π interaction (Figure 70d). Interestingly, the derivatives of β-tetralone were reduced with higher enantioselectivity (94-99% ee) using (1*R*,2*R*) complex **181** compared to β-tetralone. This may be possible due to CH-π interactions between the substituents on the α-position and -CH of η^6-arene-Ru complex (Figure 70e). To identify the dominating interaction between the established CH-π interaction and observed interaction, compound **356** was selected for the reduction. The (1*R*,2*R*) complex **181** gave high enantioselectivity (99% ee, *R* enantiomer) for compound **356**, which could arise *via* established CH-π interaction as shown in Figure 70f. Taken together, these results suggest that a cyclic ring with unsaturation or an aryl substituent at the α-position of the ketone contributes positively to the enantiocontrol of the asymmetric transfer hydrogenation by η^6-arene-Ru-TsDPEN complexes such as **181**.

2.5 Conclusion

In summary, 1,2-cyclohexanediamine derivative **260** was found to be less efficient and selective compared to 1,2-diphenyl-1,2-ethanediamine derivative **56** for the Michael addition of *trans*-β-nitrostyrene to acetone under optimised conditions. The synthesis of other derivatives of 1,2-cyclohexanediamine such as **261** and **263** was attempted, but it was not possible to prepare them. Successfully synthesized compounds **260**, **262** and **264** were used to screen for different asymmetric reactions such as Michael addition of *trans*-β-nitrostyrene to diethyl malonate, aldol reaction between 2-nitro-benzaldehyde and acetone/cyclohexanone and Henry reaction between 2-nitro-benzaldehyde and nitromethane. However, none of these compounds exhibited promising efficacy and selectivity for tested reactions.

The stable cyclic aminal **278** and similar derivatives of TsDPEN (**282**-**284**), which have structural similarities to Macmillan organocatalysts, were synthesised. Compounds **278** and **282**-**284** were successfully prepared as single diastereomers in good to high yields. For the initial study, the Diels-Alder reaction between 1,3-cyclohexadiene and acrolein was used to test compounds **278** and **282**-**284**. The hydrochloride salt of compounds **278** showed a good enantioselectivity of 72% ee (*S* enantiomer) for the reaction of 1,3-cyclohexadiene and acrolein in acetonitrile:water (95:5). On other hand, the hydrochloride salts of compounds **282** and **283** were found to be less enantioselective, giving products of 44-45% ee. The results obtained with compounds **278**, **282** and **283**, indicated that the good enantioselectivity obtained with compound **278** is mostly due to the bulkier group (-OTBDPS) present in it. The hydrochloride salt of compound **284** was found to be less stable and resulted in low enantioselectivity for the tested reaction, which is similar to that obtained using the hydrochloride salt of TsDPEN **64**.

The stable cyclic derivative **278** was screened for different asymmetric reactions. Out of these the addition reaction of aldehyde to DEAD showed a promising result. The reaction conditions were optimized using compound **278** for addition of isovaleraldehyde to DEAD, including as catalyst loading, acid loading and effect of temperature. Under the optimized reaction conditions, compounds **278** and **282**-**284** were studied for the reaction of propionaldehyde to DEAD, however compound only **278** has gave a high enantioselectivity in the tested reaction. Compound **278** was selected to test for addition of different aldehydes to DEAD. Compound **278** has gave high enantioselectivities for simple aldehydes. Compound **278** was found to be moderately selective in control of the addition of propionaldehyde to DIAD and DTAD. Moreover, compound **278** was found to be less efficient for addition of branched aldehydes (e.g. formylcyclohexane) or a ketone (acetone) to DEAD. These results show that compound **278** is good for addition of simple aldehydes to DEAD under optimized conditions.

The asymmetric transfer hydrogenation of ketones and imines were studied with compounds **299** and **302** using FA:TEA (5:2) as source of hydrogen. Moreover the transfer hydrogenation of ketone and imine using compounds **299** and **302** were also compared with the related -NH_2 (**193**) and -NH (**193a** and **181**) analogues under similar conditions. The results obtained using *N*-alkylated complexes **299** and **302** for transfer hydrogenation of acetophenone **112** show that he ketone reduction was quite slow compared to -NH_2 (**193**) and -NH (**193a** and **181**) analogues. Thus, the transfer hydrogenation of ketone appears to require -NH in the complex for the reduction to be achieved, which confirms that ketones reduction takes place *via* a six membered cyclic transition state mechanism (concerted mechanism). On the other hand, both **299** and **302** were active in reduction of imine **165** under transfer

hydrogenation conditions using FA:TEA, Which requires the protonation of imine **165** with hydrogen source (FA:TEA) followed by hydride transfer from the Ru-H formed in situ. Thus, transfer hydrogenation of imines using compounds **299** and **302** confirms an ionic or stepwise mechanism. Interestingly, both the compounds **299** and **302** were found to form the hydride intermediate quite fast using FA:TEA and this can be detected using 1H-NMR in $CDCl_3$ at δ -5.4. Moreover, hydride formation was also detected for the reduction of imine **165** using a 3 mol% loading of compounds **299** and **302**. At the same time, the reduction of imine **165** was found to be slower, which shows that rate determining step is transfer of hydride from complex to imine substrate for transfer hydrogenation using compounds **299** and **302**. Compound **302** can be applied to asymmetric reductive amination due to its preference for the reduction of imines over ketones. Unfortunately, compound **302** was found to be less enantioselective for transfer hydrogenation of imines, probably due to the steric effect of -*N*Me.

The asymmetric transfer hydrogenation of aryl alkyl ketones were reported to be highly efficient and selective using complexes **153** and **181**, which involves CH-π interaction between η^6-arene ring of Ru complex and aryl ring of substrates. At the same time transfer hydrogenation of the ketones without aryl groups were found to be much slower and less enantioselective. This can limit the substrate scope for asymmetric transfer hydrogenation of ketones and will require at least one aryl group in the substrate. A series of ketone derivatives were prepared with substitution on the α position containing a constrained cyclic group with an unsaturation, without unsaturation and an aryl substituent on the ring. These ketones were used in asymmetric transfer hydrogenation using (1*R*,2*R*) Ru-3C-tethered catalyst **181** in FA:TEA as source of hydrogen. The ketones with a constrained cyclic group with an

unsaturation or aryl substituent on the ring were reduced easily and with good-high enantioselectivities using (1*R*,2*R*) Ru-3C-tethered catalyst **181**. In contrast, asymmetric transfer hydrogenation of ketones containing a constrained cyclic group without unsaturation was less enantioselective.

These results can be explained by either (i) possible CH-π interaction between the η^6-arene ring of Ru complex and properly placed cyclic group with an unsaturation or aryl substituent in the ketone substrate, or (ii) the bridging chain present in (1*R*,2*R*) Ru-3C-tethered catalyst **181** provides the stable interaction during the catalytic cycle. To rule out the second possibility, selected compounds were used for asymmetric transfer hydrogenation using Noyori's catalyst **153** and were found to be reduced with similar enantioselectivities. Moreover, compound **356** was prepared having both aryl group next to ketone and a constrained cyclic group with an aryl substituent on the ring to identify which interaction is stronger and dominating in asymmetric transfer hydrogenation. The asymmetric transfer hydrogenation of compound **356** using (1*R*,2*R*) Ru-3C-tethered catalyst **181** showed that established CH-π interaction between η^6-arene ring of Ru complex and aryl group next to ketone is dominating (Figure 70f). At the same time, asymmetric transfer hydrogenation of substituted ketones **312**. **321** and **322** (lacking an aryl group next to the ketone) was enantioselective with high ee using (1*R*,2*R*) Ru-3C-tethered catalyst **181**. Thus, when the dominating CH-π interaction between the η^6-arene ring of Ru complex and the aryl group is absent then a suitable group with single double bond or aromatic ring can give rise to weak interaction η^6-arene ring of Ru complex (Figure 71a & 71b), followed by highly enantioselective asymmetric transfer hydrogenation.

3 Experimental

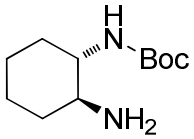
General Experimental:

All the air sensitive reactions were carried out under an argon atmosphere. NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All chemical shifts are reported in ppm downfield from TMS (Me_4Si). Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H-NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), broad singlet (br s), broad doublet (br d),and multiplet (m). Mass spectra were recorded on an Esquire 2000. High resolution mass spectra were recorded on Bruker Micro ToF. Infrared spectra were recorded on PerkinElmer spectrum100. The optical rotations were measured on Optical Activity Ltd. AA-1000 Polarimeter. The Chiral HPLC measurements were carried out on HPLC consisting of a Gilson 811B Dynamic Mixer, a Gilson 805 Monometer Module, a Gilson 305 Piston Pump, Merck-Hitachi L-4000 UV detector linked to HEWLETT PACKARD 3396 Series II integrator with CHIRAL PAK IA/IB column (0.46 cm x 25 cm). The chiral GC measurements were done on HEWLETT PACKARD 5890 linked to HEWLETT PACKARD HP3396A integrator or PERKIN-ELMER 8500 chromatography linked to PC running DataApex Clarity software with Chrompak CP-Chirasil Dex Cβ column. Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Purification of compounds was done by using flash column chromatography using silica gel of mesh size 230-400 or Florisil.

3.1 Synthesis of derivatives of 1,2-cyalcohexanediamine

3.1.1 Synthesis of (1*S*,2*S*)-*N*-(diphenylphosphinyl)-1,2-diaminocyclohexane (**260**).[252]

(1*S*,2*S*)-1-(*N*-*t*-Butyloxycarbonylamino)-2-aminocyclohexane (266).

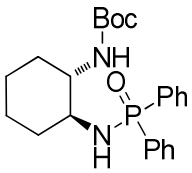


This is a known compound and the method is based on a reported synthesis.[252(b)]

To a solution of (1*S*,2*S*)-1,2-cyclohexanediamine **265** (3.133 g, 27.436 mmol) in dichloromethane (17 mL) was added dropwise a solution of Boc_2O (2.0 g, 9.164 mol, 0.33 eq) in dichloromethane (17 mL) at 20-21 ^oC over a period of 10-12 min. On addition, the reaction mixture was converted into a white emulsion. The resulting suspension was stirred at 20-21 ^oC for 18 h. The reaction mixture was then diluted with distilled water (15 mL) and extracted with dichloromethane (2 x 20 mL). The organic layer was separated and the solvent removed on a rotavapor. The residue was dissolved in a mixture of diethyl ether: distilled water (1:1) (5 mL) and the aqueous layer was acidified to pH 5 by using 4M HCl solution. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The aqueous phase was basified to pH 11 by using 2N NaOH solution and extracted with EtOAc (6 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give compound (1*S*,2*S*)-1-(*N*-*t*-butyloxycarbonylamino)-2-aminocyclohexane **266** as an off white solid (1.600 g, 7.477 mmol, 81%). δ_H (300 MHz, $CDCl_3$) 4.41 (1H, br s, -N*H*Boc), 3.11 (1H, m, -C*H*NHBoc), 2.34 (1H, dt, *J* 10.2, 5.2, -C*H*NH_2), 1.95 (2H,

m, -CH_2 cycl), 1.67 (2H, m, -CH_2 cycl), 1.45 (2H, s, -NH_2), 1.42 (9H, s, -C(CH_3)$_3$), 1.34-0.97 (4H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 156.15, 68.36, 57.63, 55.66, 35.19, 32.91, 28.40(3C), 25.19, 25.08; ESI-MS $[M+H]^+$ 215.1. The spectroscopic data were in agreement with literature values.[252(b)]

(1*S*,2*S*)-1-(*N*-*t*-Butyloxycarbonylamino)-2-(*N*'-diphenylphosphonamide)-cyclohexane (267).

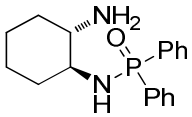


The method is based on a reported synthesis; however the compound has not been fully characterised.[252(a)]

To a solution of (1*S*,2*S*)-1-(*N*-*t*-butyloxycarbonylamino)-2-aminocyclohexane **266** (1.350 g, 6.308 mmol) in dichloromethane (48 mL) was added diisopropyl ethyl amine (1.923 mL, 11.039 mmol, 1.75 eq) under an inert atmosphere and cooled to -30 ^oC. To this, diphenylphosphinic chloride (1.318 mL, 6.920 mmol, 1.09 eq) was added dropwise. The resulting mixture was stirred at 20-21 ^oC for 2 h. The reaction mixture was diluted with dichloromethane (70 mL). The organic layer was washed with 1N HCl solution (40 mL), saturated $NaHCO_3$ solution (40 mL), distilled water (40 mL) and brine solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a solid residue. The solid was purified by flash column chromatography to give compound (1*S*,2*S*)-1-(*N*-*t*-butyloxycarbonylamino)-2-(*N*'-diphenylphosphonamide)-cyclohexane **267** as a white solid (2.46 g, 5.942 mmol, 94%). Mp 208-210 ^oC; $[\alpha]_D^{15}$ = -13.9 (*c* 1 in $CHCl_3$); ν_{max} 3381, 2929, 2359, 2341, 1707, 1696, 1544, 1527, 1439, 1417, 1390 cm^{-1}; δ_H (300

MHz, $CDCl_3$) 7.90 (2H, m, *o*-C*H* of Ph), 7.76 (2H, m, *o*-C*H* of Ph), 7.48-7.37 (6H, m, *m*,*p*-C*H* of both Ph), 5.34 (1H, d, *J* 7.8, -N*H*Boc), 3.35-3.19 (2H, m, -C*H*NHBoc, -N*H*P(O)Ph_2), 2.79 (1H, m, -C*H*NHP(O)Ph_2), 2.08 (2H, m, -CH_2 cycl), 1.61 (2H, m, -CH_2 cycl), 1.48 (9H, s, -C(CH_3)$_3$), 1.40-1.10 (4H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 132.31, 132.21, 131.86, 131.83, 131.78(2C), 131.74(2C), 128.51, 128.34, 55.69, 55.48, 36.18, 33.21, 28.53(3C), 25.05, 24.83; m/z ESI-MS $[M+H]^+$ 415.2; HRMS found 415.2106 (requires $C_{23}H_{31}N_2O_3P+H^+$ 415.2145, error = -3.64 ppm). The spectroscopic data were in agreement with literature values.[252(a)]

(1*S*,2*S*)-*N*-(Diphenylphosphinyl)-1,2-diaminocyclohexane (280).



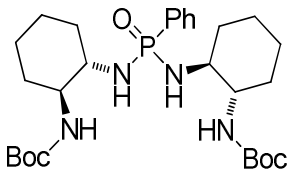
This is a known compound and the method is based on a reported synthesis.[252(a)]

To a solution of (1*S*,2*S*)-1-(*N*-*t*-butyloxycarbonylamino)-2-(*N*'-diphenylphosphonamide)-cyclohexane **267** (2.30 g, 5.556 mmol) in dichloromethane (50 mL) was added trifluoroacetic acid (8.25 mL, 111.12 mmol, 20 eq) dropwise over a period of 10-12 min. The resulting mixture was stirred at 20-21 ^oC for 1.5 h. To the reaction mixture was added TEA (15.46 mL, 111.12 mmol, 20 eq) dropwise at 0 ^oC over a period of 10 min to give a clear solution. The reaction mixture was diluted with dichloromethane (50 mL) and distilled water (50 mL). The organic layer was separated and washed with distilled water (2 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The solid residue was purified by flash column chromatography to give (1*S*,2*S*)-*N*-(diphenylphosphinyl)-1,2-diaminocyclohexane **260** as an off white solid (1.20 g, 3.822 mmol, 68%). Mp 154-156 ^oC; $[\alpha]_D^{15}$ = +7.4 (*c* 0.505 in $CHCl_3$); ν_{max} 3262,

3054, 2931, 2857, 2360, 1686, 1522, 1438 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.94-7.84 (4H, m, *o*-C*H* of Ph), 7.49-7.40 (6H, m, *m*,*p*-C*H* of Ph), 2.94 (1H, m, -C*H*NHP(O)Ph_2), 2.63-2.50 (1H, m, -C*H*NH_2), 2.39-2.31 (1H, m, -CH_2 cycl), 2.06 (1H, m, -CH_2 cycl), 1.90 (1H, m, -N*H*P(O)Ph_2), 1.61 (3H, m, -NH_2, -CH_2 cycl), 1.24-0.97 (5H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 131.77, 131.64, 131.31, 131.18(3C), 127.99(2C), 127.82(2C), 58.37, 56.43, 34.64, 34.38, 24.77, 24.37; δ_P (121 MHz, $CDCl_3$) 22.7318, m/z ESI-MS $[M+H]^+$ 315.1; HRMS found 315.1621 ($C_{18}H_{23}N_2OP+H^+$ requires 315.1582, error = -3.88 ppm); The X-ray Structure was obtained (more details in Appendix 5.1.1). The spectroscopic data were in agreement with literature values.[252(a)]

3.1.2 Synthesis of (1*S*,2*S*)-phenylphosphonic bis(1-amino-2-cyclohexylamide) (261).

(1*S*,2*S*)-Phenylphosphonic bis[1-(*N*-*t*-butyloxycarbonylamino)-2-cyclohexylamide] (269).

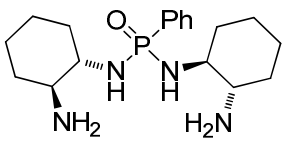


This is a novel compound and the method is based on a reported synthesis.[253]

To a solution of phenylphosphonic dichloride (0.161 mL, 1.135 mmol, 0.486 eq) in dichloromethane (10 mL) was added TEA (1.60 mL, 11.493 mmol, 4.92 eq) and DMAP (13.8 mg, 0.113 mmol, 0.0486 eq) at 0 ^oC under inert atmosphere. To this, a solution of (1*S*,2*S*)-1-(*N*-*t*-butyloxycarbonylamino)-2-aminocyclohexane **266** (0.500 g, 2.336 mmol) dichloromethane (10 mL) was added dropwise. The resulting mixture was stirred at 20-21 ^oC for 3.5 h. The reaction mixture was diluted with

dichloromethane (30 mL). The organic layer was washed with distilled water (20 mL), saturated $NaHCO_3$ solution (20 mL), distilled water (20 mL), and brine solution. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure on a rotavapor to give an oil. The oil was purified by flash column chromatography and pure compound was eluted out in EtOAc. The pure compound (1*S*,2*S*)-phenyl phosphonic bis[1-(*N*-*t*-butyloxycarbonylamino)-2-cyclohexylamide] **269** was obtained as an oil (0.300 g, 0.545 mmol, 47%). $[\alpha]_D^{28}$ = -6.19 (*c* 0.105 in $CHCl_3$); ν_{max} 3376, 3312, 3221, 3144, 2929, 2857, 1708, 1684, 1512, 1450, 1439, 1237, 1126, 1110, 1091, 1017, 920, 759, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82 (2H, m, *o*-C*H* of Ph), 7.44 (3H, m, *m,p* -C*H* of Ph), 6.12 (1H, br s, -N*H*), 5.48 (1H, br s, -N*H*), 3.15 (2H, m, -C*H*NHBoc), 3.04-2.57 (4H, m, -C*H* cycl), 2.21 (1H, br d, -CH_2 cycl), 2.07 (2H, m, -CH_2 cycl), 1.87 (1H, br d, -CH_2 cycl), 1.61 (4H, m, -N*H* Phosphonamide, -CH_2 cycl), 1.47 (9H, s, -C(CH_3)$_3$), 1.41 (9H, s, -C(CH_3)$_3$), 1.34-0.99 (8H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 130.98, 130.89, 130.76, 127.77, 127.59, 71.70, 71.63, 55.28, 35.23, 34.79, 28.01, 27.85, 27.44, 27.33, 26.07, 25.83, 24.69, 24.05, 23.90, 18.32; m/z ESI-MS $[M+H]^+$ 551.2; HRMS found 551.3365 ($C_{28}H_{47}N_4O_5P+H^+$ requires 551.3357, error = -1.5 ppm).

Attempted synthesis of (1*S*,2*S*)-phenylphosphonic bis(1-amino-2-cyclohexylamide) (261).

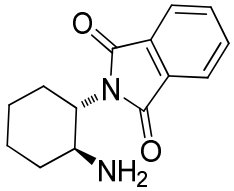


Using TFA: To a solution of (1*S*,2*S*)-phenylphosphonic bis[1-(*N*-*t*-butyloxycarbonylamino)-2-cyclohexylamide] **269** (25 mg, 0.0454 mmol) in dichloromethane (1 mL) was added TFA (33.7 µL, 0.454 mmol, 10 eq) dropwise

over a period of 2-3 min. The resulting mixture was stirred at 19-20 ^{o}C for 1 h. To the reaction mixture was added TEA (63.4 µL, 0.454 mmol, 10 eq) dropwise at 0 ^{o}C over a period of 2-3 min to give a clear solution. The reaction mixture was diluted with dichloromethane (5 mL) and distilled water (5 mL). The organic layer was separated and washed with distilled water (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give an oil. The oil was analysed by ^{1}H-NMR and ESI-MS. ^{I}H-NMR corresponded to TEA only.

Using $ZnBr_2$[254]: To a solution of (1*S*,2*S*)-phenylphosphonic bis[1-(*N*-*t*-butyloxycarbonylamino)-2-cyclohexylamide] **269** (0.150 g, 0.273mmol) in dichloromethane (3.5 mL) was added zinc (II) bromide (0.307 g, 1.364 mmol, 5.02 eq) The resulting mixture was stirred at 19-20 ^{o}C for 24 h. The reaction mixture was diluted with dichloromethane (20 mL) and distilled water (20 mL). The organic layer was separated and washed with distilled water (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give solid residue (30 mg, 0.066 mmol, 24%). The solid was analysed by ^{1}H-NMR and ESI-MS. The ^{I}H-NMR spectrum was quite complex and product could not be identified. ESI-MS $[M+H]^+$ 451.2 corresponded to mono Boc- compound **270** instead of required compound **261**.

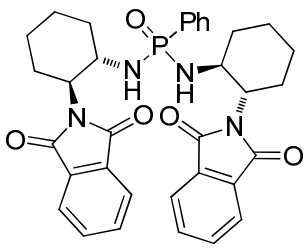
(1*S*,2*S*)-*N*-Phthaloyl-1,2-diaminocyclohexane (271).



This is a known compound and the method is based on a reported synthesis.[255]

A solution of *p*-toluenesulfonic acid monohydrate (1.902 g, 10.0 mmol) in *p*-xylene (50 mL) was dehydrated by azeotropic distillation. The resulting light brown solution was cooled to 20-21 ^{o}C. To this solution was added (1*S*,2*S*)-1,2-cyclohexanediamine **265** (1.14 g, 10.0 mmol) followed by phthalic anhydride (1.48 g, 10.0 mmol) to give a suspension. The mixture was heated at 132-135 ^{o}C to give a homogenous solution at which point the solid was started separating out. The reaction mixture was cooled to 25 ^{o}C, filtered under suction, washed with mixture of *p*-xylene-hexane and dried to give the *p*-TsOH salt (4.10 g, 9.25 mmol, 98%). The salt (4.0 g, 9.615 mmol) in dichloromethane (35 mL) was stirred overnight with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated on a rotavapor to give compound (1*S*,2*S*)-*N*-phthaloyl-1,2-diaminocyclohexane **271** as a light brown solid (2.15 g, 8.811 mmol, 91%). δ_H (300 MHz, $CDCl_3$) 7.81 (2H, m, *o*-C*H* of Ph), 7.69 (2H, m, *m*-C*H* of Ph), 3.83 (1H, dt, *J* 11.4, 3.6, -C*H*NPhth), 3.45 (1H, dt, *J* 10.8, 4.2, -C*H*NH_2), 2.18 (1H, br d, -CH_2 cycl), 2.06 (1H, br d, -CH_2 cycl), 1.90-1.70 (4H, m, -NH_2, -CH_2 cycl), 1.53-1.10 (4H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 168.18(2C), 133.21(2C), 131.32(2C), 122.51(2C), 57.45, 50.21, 35.56, 28.70, 24.95, 24.39; m/z ESI-MS $[M+H]^+$ 245.0. The spectroscopic data were in agreement with literature values.[255]

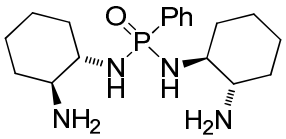
(1*S*,2*S*)-Phenylphosphonic bis(*N*-phthaloyl-1-cyclohexyl-2-amide) (272).



This is a novel compound and the method is based on a reported synthesis.[253]

To a solution of phenylphosphonic dichloride (0.290 mL, 1.992 mmol, 0.486 eq) in dichloromethane (20 mL) was added TEA (2.805 mL, 20.162 mmol, 4.92 eq) and DMAP (24 mg, 0.199 mmol, 0.0486 eq) at 0 ^{o}C under an inert atmosphere. To this, a solution of (1*S*,2*S*)-*N*-Phthaloyl-1,2-diaminocyclohexane **271** (1.0 g, 4.098 mmol) in dichloromethane (20 mL) was added dropwise. The resulting mixture was stirred at 20-21 ^{o}C for 18 h. The reaction mixture was diluted with distilled water (50 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layer was washed saturated $NaHCO_3$ solution (20 mL), distilled water (2 x 50 mL), and brine solution. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure on a rotavapor to give a brown oil. The oil was purified by flash column chromatography and a pure compound was eluted in MeOH:$CHCl_3$ (1:9). The pure compound (1*S*,2*S*)-phenylphosphonic bis(*N*-phthaloyl-1-cyclohexyl-2-amide) **272** was obtained as an oil (0.600 g, 0.984 mmol, 48%). $[\alpha]_D^{28}$ = +84.5 (*c* 0.110 in $CHCl_3$); ν_{max} 3348, 2932, 2856, 1765, 1700, 1390, 1372, 1192, 1152, 1074, 904, 716, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.90 (2H, br s, *o*-C*H* of Phth), 7.81 (2H, m, *o*-C*H* of Phth), 7.53 (2H, m, *m* -C*H* of Phth), 7.47 (2H, m, *m* -C*H* of Phth), 7.08 (2H, m, *o*-C*H* of Ph), 6.85 (1H, dt, *J* 7.5, 1.5, *p*-C*H* of Ph), 6.69 (2H, dt, *J* 7.5, 3.6, -C*H* of Ph), 3.78 (2H, m, -2 x CHN*H*), 3.65 (2H, m, -C*H*NPhth), 2.29-2.06 (6H, m, -CH_2 cycl), 1.78 (3H, br d, -CH_2 cycl), 1.59 (2H, br d, -CH_2 cycl), 1.44-1.08 (7H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 168.39(4C), 133.37, 132.54(2C), 130.26, 130.14, 129.93, 126.96, 126.78, 122.75, 122.17, 55.78, 55.68, 55.62, 55.55, 50.42, 36.34, 36.28, 28.95, 28.38; m/z ESI-MS $[M+H]^+$ 611.2; HRMS found 633.2236 ($C_{34}H_{35}N_4O_5P$+Na requires 633.2237, error = 0.3 ppm).

Attempted synthesis of (1*S*,2*S*)-phenylphosphonic bis(1-amino-2-cyclohexylamide) (261).

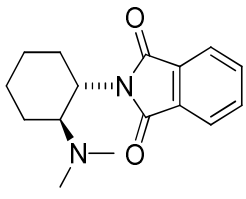


The method is based on a reported synthesis.[253]

To a solution of compound **272** (0.600 g, 0.984 mmol) in ethanol (15 mL) was added hydrazine hydrate (0.138 mL, 4.488 mmol, 4.50 eq) at 20-21 ^{o}C. The reaction mixture was slowly heated to reflux at 77-78 ^{o}C and during 10 min the solid was started separating out. The reaction mixture was refluxed for additional 2 h. The reaction mixture was cooled to 20 ^{o}C, diluted with diethyl ether (10 mL) and a solid was filtered off. The filtrate was concentrated under reduced pressure to give a brown oil. The brown oil (0.400 g) was analysed by ^{1}H-NMR and ESI-MS. Both data do not comply for formation of required product and ESI-MS shows the formation of low molecular weight product (282). δ_H (300 MHz, $CDCl_3$) 7.84 (2H, br s, *o*-CH of Ph), 7.49 (3H, m, *m*,*p*-CH of Ph), 4.11 (2H, m), 2.64 (2H, m), 2.28 (1H, m), 1.90 (2H, m), 1.30 (3H, m), 1.26-1.01 (4H, m); ^{31}P-NMR δ_P (300 MHz, $CDCl_3$) 21.94, 21.70; m/z ESI-MS $[M+H]^+$ 283.1.

3.1.3 Synthesis of (1*S*,2*S*)-*N*,*N*-dimethyl-*N*'-(diphenylphosphinyl)-1,2-diaminocyclohexane (262).[252a, 255]

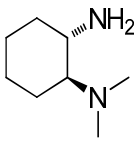
(1*S*,2*S*)-*N*,*N*-Dimethyl-*N*'-phthaloyl-1,2-diaminocyclohexane (273).



This is a known compound and the method is based on a reported synthesis.[255]

A mixture of (1*S*,2*S*)-*N*-phthaloyl-1,2-diaminocyclohexane **271** (2.00 g, 8.196 mmol), 80% formic acid (3.4 mL) and 37% formaldehyde solution (1.46 mL, 18.08 mmol, 2.20 eq) was stirred under reflux (heating temperature 125 ^{o}C) for 6 h. The reaction mixture was cooled to 25-28 ^{o}C and concentrated under reduced pressure to give a brown residue. The residue was taken up in dichloromethane (50 mL) and was added slowly to saturated $NaHCO_3$ solution (15 mL) with stirring. The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give brown solid. The solid was crystallised from benzene-hexane to give compound (1*S*,2*S*)-*N*,*N*-dimethyl-*N*'-phthaloyl-1,2-diaminocyclohexane **273** as off white solid (1.25 g, 4.595 mmol, 56%). δ_H (300 MHz, $CDCl_3$) 7.78 (2H, m, *o*-C*H* of Ph), 7.65 (2H, m, *m*-C*H* of Ph), 4.08 (1H, dt, *J* 11.5, 3.6, -C*H*NPhth), 3.28 (1H, dt, *J* 11.4, 3.6, -C*H*N(CH_3)$_2$), 2.12 (6H, s, -N(CH_3)$_2$), 1.97-1.70 (5H, m, -CH_2 cycl), 1.40-1.11(3H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 168.08, 132.94, 131.63, 122.36, 61.54, 51.63, 39.65, 29.64, 25.14, 24.48, 22.13; m/z ESI-MS $[M+H]^+$ 273.1. The spectroscopic data were in agreement with literature values.[255]

(1*S*,2*S*)-*N*,*N*-Dimethyl-1,2-diaminocyclohexane (274).

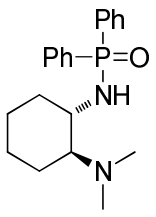


This is a known compound and the method is based on a reported synthesis.[255]

To a solution of (1*S*,2*S*)-(+)-*N*,*N*-dimethyl-*N*'-phthaloyl-1,2-diaminocyclohexane **273** (1.17 g, 5.032 mmol) in ethanol (20 mL) was added hydrazine hydrate (0.603 mL, 19.376 mmol, 3.85 eq) at 20-21 ^{o}C. The reaction mixture was slowly heated to reflux

at 77-78 ^{o}C and during 10 min the solid started separating out. The reaction mixture was refluxed for additional 2 h. The reaction mixture was cooled to 20 ^{o}C, diluted with diethyl ether (10 mL) and solid was filtered off. The filtrate was concentrated under reduced pressure to give a brown oil. The oil was dissolved in a mixture of diethyl ether: distilled water (1:1) (5 mL) and the aqueous layer was acidified to pH 5 using 4M HCl solution. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The aqueous phase was basified to pH 11 by using 2N NaOH solution and extracted with EtOAc (6 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give compound (1*S*,2*S*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **274** as brown oil (0.386 g, 2.718 mmol, 63%). δ_H (300 MHz, $CDCl_3$) 2.58 (1H, dt, *J* 10.2, 4.2, -C*H*NH_2), 2.24 (6H, s, -N(C*H*$_3$)$_2$), 2.05 (1H, m, -C*H*N$(CH_3)_2$), 1.95 (1H, m, -C*H*$_2$ cycl), 1.82-1.63 (5H, m, -N*H*$_2$, -C*H*$_2$ cycl), 1.27-1.02 (4H, m, -C*H*$_2$ cycl); δc (75 MHz, $CDCl_3$) 69.73, 51.40, 40.19(2C), 35.11, 25.59, 25.07, 20.57; m/z ESI-MS $[M+H]^+$ 143.1. The spectroscopic data were in agreement with literature values.[255]

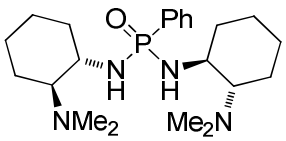
(1*S*,2*S*)-*N*,*N*-Dimethyl-*N*'-(diphenylphosphinyl)-1,2-diaminocyclohexane (262).[252(a)]



This is a known compound and the method is based on a reported synthesis.[252(a)]

To a solution of (1*S*,2*S*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **274** (0.35 g, 2.465 mmol) in dichloromethane (20 mL) was added diisopropyl ethyl amine (0.751 mL, 0.515 mmol, 1.75 eq) under inert atmosphere and cooled to -30 ^{o}C. To this, diphenylphosphinic chloride (0.515 mL, 2.705 mmol, 1.097 eq) was added dropwise. The resulting mixture was stirred at 20-21 ^{o}C for 2 h. The reaction mixture was diluted with dichloromethane (70 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL), distilled water (20 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure on a rotavapor to give compound (1*S*,2*S*)-*N*,*N*-dimethyl-*N'*-(diphenylphosphinyl)-1,2-diaminocyclohexane **262** as a off white solid (0.400 g, 1.169 mmol, 47%). Mp 104-106 ^{o}C; $[\alpha]_D^{15}$ = +42.75 (*c* 0.504 in $CHCl_3$); ν_{max} 3315, 3211, 2927, 2850, 2775, 2369, 1448, 1435, 1190, 1177, 1122, 1107, 1096, 751, 723, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88 (2H, m, *o*-C*H* of -$POPh_2$), 7.77 (2H, m, *o*-C*H* of -$POPh_2$), 7.52-7.39 (6H, m, *m*,*p*-C*H* of-$POPh_2$), 4.75 (1H, d, *J* 7.2, -N*H*$POPh_2$), 3.14 (1H, m, -C*H*NH$POPh_2$), 2.27 (1H, br d, -C*H*N$(CH_3)_2$), 2.20 (6H, s, -N(CH_3)$_2$), 2.14 (1H, br d, -CH_2 cycl), 1.73 (2H, br d, -CH_2 cycl), 1.49 (1H, br d, -CH_2 cycl), 1.27-1.02 (4H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 164.22(2C), 132.15, 132.03, 131.49, 131.36(3C), 128.52, 128.35, 128.29, 128.12, 68.04, 67.93, 52.22, 40.00, 34.15, 25.28, 24.49, 20.69; m/z ESI-MS $[M+H]^+$ 343.1; HRMS found 343.1925 ($C_{20}H_{27}N_2OP+H^+$ requires 343.1934, error = 2.43 ppm). The spectroscopic data were in agreement with literature values.[252(a)]

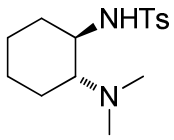
3.1.4 Attempted Synthesis of (1*S*,2*S*)-phenylphosphonic bis(*N*,*N*-dimethyl-cyclohexyl-2-amide) (263).



The procedure is same as described for the synthesis of compound (1*S*,2*S*)-phenyl phosphonic bis[1-(*N*-*t*-butyloxycarbonylamino)-2-cyclohexylamide] **269**.

The crude residue was purified by scratching in hexane to give the solid (0.180 g). The solid was analysed by ^{1}H-MNR and ESI-MS. ^{1}H-MNR was complex, the compound was analysed by ^{31}P-NMR δ_P (300 MHz, $CDCl_3$) 21.14, 12.65; m/z ESI-MS $[M+H]^+$ 547.2; HRMS found 547.2960 ($C_{28}H_{45}N_4O_3P_2$ H^+ requires 547.2961, error = 0.27 ppm).

3.1.5 (1*R*,2*R*)-*N*,*N*-Dimethyl-*N'*-tosyl-1,2-diaminocyclohexane (264).



This is a known compound, but not fully characterized.[84] The method is based on a reported synthesis.[255]

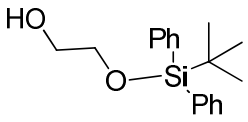
A mixture of (1*R*,2*R*)-*N*-tosyl-1,2-diaminocyclohexane **148** (1.00 g, 2.725 mmol), 80% formic acid (1.54 mL) and 37% formaldehyde solution (0.664 mL, 8.193 mmol, 2.20 eq) was stirred under reflux (heating temperature 125 ^{o}C) for 6 h. The reaction mixture was cooled to 25-28 ^{o}C and concentrated under reduced pressure to give a residue. The residue was dissolved in dichloromethane (50 mL) and was added slowly to a saturated $NaHCO_3$ solution (15 mL) with stirring. The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give a white solid. The solid was crystallised from diethyl ether to give compound

(1*R*,2*R*)-*N*,*N*-dimethyl-*N*'-tosyl-1,2-diaminocyclohexane **264** as a colourless crystalline solid (0.900 g, 3.040 mmol, 81%). Mp 96-98 ^{o}C; $[\alpha]_D^{15}$ = -81.7 (*c* 0.500 in $CHCl_3$); ν_{max} 3168, 2930, 2866, 2369, 1598, 1453, 1395, 1381, 1342, 1158, 1087, 1040, 812, 713 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.1, *o*-C*H* of -SO_2PhCH_3), 7.29 (2H, d, *J* 7.8, *m*-C*H* of -SO_2PhCH_3), 6.08 (1H, br s, -N*H*Ts), 2.60 (1H, dt, *J* 10.35, 3.9, -C*H*NHTs), 2.42 (3H, s, -SO_2PhCH_3), 2.36 (1H, br d, -CH_2 cycl), 2.14 (1H, dt, *J* 11.1, 3.0, -C*H*N$(CH_3)_2$), 1.92 (6H, s, -N$(CH_3)_2$), 1.75 (2H, br d, -CH_2 cycl), 1.64 (1H, m, -CH_2 cycl), 1.32-0.89 (4H, m, -CH_2 cycl); δc (75 MHz, $CDCl_3$) 129.51(2C), 127.37(2C), 66.18, 54.03, 39.61(2C), 32.58, 25.04, 24.21, 21.55, 20.98; m/z ESI-MS $[M+H]^+$ 297.1; HRMS found 297.1630 ($C_{15}H_{24}N_2O_2+H^+$ requires 297.1631, error = 0.39 ppm).

3.2 Synthesis of derivatives of 1,2-diphenylethanediamine

3.2.1 Synthesis of (4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine (278).

2-(*t*-Butyldiphenylsilyloxy) ethanol (**287).**

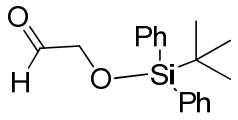


This is a known compound and the method is based on a reported synthesis.[256]

To a solution of ethylene glycol **286** (4.86 mL, 87.288 mmol, 6.0 eq) in dry THF (75 mL) was added imidazole (1.090 g, 16.017 mmol) under inert atmosphere and stirred for 5-7 min. To this *t*-butyldiphenylsilyl chloride (3.78 mL, 14.548 mmol, 1.0 eq) was added dropwise. The resulting hazy solution was stirred at 20-21 ^{o}C for 24 h under inert atmosphere. The reaction mixture was quenched with mixture of distilled

water and diethyl ether (80 mL, 1:1). The organic layer was separated and aqueous layer was extracted with diethyl ether (3 x 40 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using pentane: EtOAc (4:1) to give compound 2-(*t*-butyldiphenylsilyloxy) ethanol **287** as an oil (3.80 g, 12.667 mmol, 87%). ν_{max} 3491, 3071, 2931, 2858, 1589, 1472, 1427, 1107, 1048, 937, 822, 736, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (4H, dd, *J* 7.5, 1.5, *o*-C*H* of both Ph), 7.41 (6H, m, *m,p*-C*H* of both Ph), 3.76 (2H, m, -CH_2-OTBDPS), 3.69 (2H, br s, -CH_2-OH), 2.14 (1H, br s, -O*H*), 1.06 (9H, s, -C$(CH_3)_3$); δc (300 MHz, $CDCl_3$) 134.92(4C), 132.63(2C), 129.21(2C), 127.16(4C), 64.36, 63.12, 26.23(3C), 18.77; m/z ESI-MS $[M+Na]^+$ 323.1. The spectroscopic data were in agreement with literature values.[256]

_t_-Butyldiphenylsiloxy acetaldehyde (276).

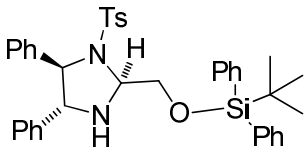


This is a known compound and the method is based on a reported synthesis.[257]

A solution of oxalyl chloride (2 M solution in DCM) (7.4 mL, 14.80 mmol, 1.2 eq) into dry DCM (70 mL) was cooled to -78 ^oC under inert atmosphere. To this DMSO (2.10 mL, 29.60 mmol, 2.4 eq) was added dropwise at -78 ^oC over a period of 10 min followed by solution of compound 2-(*t*-butyldiphenylsilyloxy) ethanol **287** (3.70 g, 12.333 mmol, 1.0 eq) into dry DCM (30 mL) over a period of 20-25 min by maintaining temp below -70 ^oC. The resulting suspension was stirred at -78 ^oC for 30 min and quenched with TEA (8.58 mL, 61.665 mmol, 5.0 eq). The reaction mixture was brought to 20-21 ^oC and stirred for 30 min. The reaction mixture was concentrated on a rotavapor to give a residue. The residue was stirred in

hexane:EtOAc (4:1) and filtered through bed of silica. The filtrate was concentrated to give a yellow oil. The crude oil was purified by column chromatography using mobile phase hexane:EtOAc (92:8) to give compound *t*-butyldiphenylsiloxy acetaldehyde **276** as yellowish oil (2.80 g, 9.396 mmol, 76%). ν_{max} 2957, 2932, 2891, 2858, 1737, 1472, 1463, 1427, 1105, 822, 737, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.72 (1H, s, -C*H*O), 7.65 (4H, m, *o*-C*H* of both Ph), 7.42 (6H, m, *m*,*p*-C*H* of both Ph), 4.21 (2H, s, -CH_2), 1.10 (9H, s, -C(CH_3)$_3$); δc (75 MHz, $CDCl_3$) 201.12, 134.90(4C), 131.87(2C), 129.46(2C), 127.32(4C), 69.38, 26.09(3C), 18.65; m/z ESI-MS $[M+H]^+$ 299.1. The spectroscopic data were in agreement with literature values.[257]

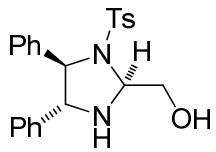
(4*R*,5*R*)-2-[(*t*-Butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine (278).



To a solution of (1*R*,2*R*)-(-)-TsDPEN **64** (0.922 g, 2.516 mmol) into dry MeOH (10 mL) was added MS 4Å (1 g) under inert atmosphere. To this, a solution of compound *t*-butyldiphenylsiloxy acetaldehyde **276** (0.9 g, 3.02 mmol, 1.2 eq) in dry MeOH (10 mL) was added dropwise at 20-21 ^oC followed by acetic acid (170 µL, 2.966 mmol, 1.179 eq). The resulting mixture was stirred at 20-21 ^oC for 4 h during which time a white solid was separated out in the reaction mixture. The solid was filtered and washed with methanol. The solid was taken up in DCM (40 mL), filtered and the filtrate was evaporated on rotavapor to give a white solid. The solid was purified by column chromatography using DCM to give compound **(**4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **278** as white solid

(1.3 g, 2.012 mmol, 80%). Mp 150-152 ^{o}C; $[\alpha]_D^{15}$ = -31.9 (*c* 0.630 in $CHCl_3$); ν_{max} 3312, 3020, 2957, 2859, 1598, 1494, 1460, 1447, 1428, 1346, 1305, 1161, 1106, 1028, 1036, 983, 850, 836, 804, 761, 730, 702, 666, 653 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (4H, m, *o*-C*H* of -OTBDPS), 7.51 (2H, d, *J* 8.1, *o*-C*H* of -SO_2PhCH_3), 7.40 (6H, m, *m*,*p*-C*H* of -OTBDPS), 7.24-7.13 (10H, m, *o*,*m*,*p*-C*H* of both -Ph), 6.90 (2H, dd, *J* 7.5, 1.2, *m*-C*H* of -SO_2PhCH_3), 4.90 (1H, m, -C*H*-CH_2OTBDPS), 4.47 (1H, d, *J* 6.0, -C*H*-NTs-), 4.15 (2H, dd, *J* 110.5, 6.3, -C*H*-NH- and -CH_2-OTBDPS), 4.06 (1H, dd, *J* 10.8, 3.3, -CH_2-OTBDPS), 2.80 (1H, br s, -N*H*), 2.39 (3H, s, -SO_2PhCH_3), 1.09 (9H, s, -C(CH_3)$_3$); δc (75 MHz, $CDCl_3$) 143.02, 139.18, 138.11, 135.11(2C), 135.07(2C), 133.32, 132.99, 132.43(2C), 129.25(2C), 128.90(2C), 127.83(2C), 127.71(4C), 127.23(2C), 127.19, 126.94, 126.86, 126.26(2C), 126.11(2C), 76.88, 70.44, 68.44, 64.38, 26.34(3C), 20.95, 18.67; m/z ESI-MS $[M+H]^+$ 647.3; HRMS found 647.2770 ($C_{39}H_{42}N_2O_3SSi$ H^+ requires 647.2758, error = -1.9 ppm).

3.2.2 Synthesis of (4*R*,5*R*)-4,5-diphenyl-1-tosylimidazolidine-2-methanol (282).



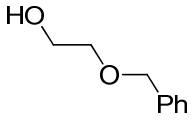
This is a novel compound and the method is based on a reported synthesis.[258]

To a solution of compound (4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **278** (1.0 g, 1.548 mmol) in dry THF (10 mL) was added TBAF (1 M solution in THF) (2.322 mL, 2.322 mmol, 1.5 eq) at 0 ^{o}C. The resulting mixture was stirred at 20-21 ^{o}C for 24 h. The reaction mixture was concentrated on a rotavapor to give a residue. The residue was purified by column

chromatography using hexane: EtOAc (1:1) to give compound (4*R*,5*R*)-4,5-diphenyl-1-tosylimidazolidine-2-methanol **282** as a white solid (0.540 g, 1.323 mmol, 85%). Mp 154-156 ^{o}C; $[\alpha]_D^{15}$ = -89.91 (*c* 0.585 in $CHCl_3$); ν_{max} 3494, 3322, 3288, 2923, 1597, 1494, 1449, 1339, 1325, 1151, 1090, 1061, 1015, 965, 812, 728, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.1, *o*-C*H* of -SO_2PhCH_3), 7.22 (10H, m, *o,m,p*-C*H* of of both -Ph), 6.93 (2H, dd, *J* 7.5, 1.5, *m*-C*H* of -SO_2PhCH_3), 5.02 (1H, br s, -C*H*-CH_2OH), 4.59 (1H, d, *J* 7.2, -C*H*-NTs-), 4.32-4.21 (1H, br s, -C*H*-NH-), 3.92 (2H, br m, -C*H*$_2$OH), 2.54 (1H, br s, -O*H*), 2.42 (3H, s, -SO_2PhCH_3), 2.33 (1H, br s, -C(C*H*$_3$)$_3$); δc (75 MHz, $CDCl_3$) 144.09, 139.27, 137.44, 134.07, 129.76(2C), 128.82(2C), 128.53(2C), 128.10, 127.81(2C), 127.71, 126.78(2C), 126.50(2C), 77.95, 71.14, 69.95, 63.67, 21.58; m/z ESI-MS $[M+H]^+$ 409.5; HRMS found 409.1577 ($C_{23}H_{24}N_2O_3S$ H+ requires 409.1580, error = 0.9 ppm).

3.2.3 Synthesis of (4*R*,5*R*)-2-[(benzyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine (283).

2-(Benzyloxy)ethanol (288).

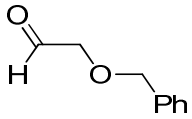


This is a known compound and the method is based on a reported synthesis.[259]

To a solution of ethylene glycol (48.91 mL, 877.04 mmol, 10 eq) in DMF:MeOH (50 mL, 1:1) was added NaH (5.12 g, 171.023 mmol, 1.95 eq) portionwise over a period of 20-25 min. The resulting hazy solution was stirred at 20-21 ^{o}C for 17 h under inert atmosphere. To this, benzyl bromide (10.43 mL, 87.704 mmol, 1.0 eq) was added dropwise and the resulting mixture was stirred at 21-22 ^{o}C for 24 h. The

reaction mixture was quenched with 10% HCl solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude oil. The oil was purified by fractional distillation at 78-90 ^oC at 1.5 mbar to give compound 2-(benzyloxy)ethanol **288** as a colourless oil (3.8 g, 25.00 mmol, 28%). ν_{max} 3388, 2928, 2866, 1718, 1662, 1453, 1066, 1027, 888, 736, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (5H, m, -C_6H_5), 4.56 (2H, s, -OCH_2Ph), 3.76 (2H, t, *J* 4.5, -CH_2-OCH_2Ph), 3.60 (2H, t, *J* 4.5, -CH_2OH), 2.16 (1H, br s, -O*H*); δc (75 MHz, $CDCl_3$) 132.27, 127.87, 127.23, 72.69, 70.79, 61.25; m/z ESI-MS $[M+Na]^+$ 175.0. The spectroscopic data were in agreement with the literature values. [259]

2-(Benzyloxy)acetaldehyde (**289).**

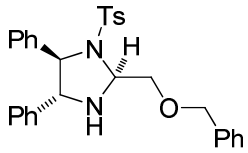


This is a known compound and the method is based on a reported synthesis.[260]

A solution of oxalyl chloride (2 M solution in DCM) (7.89 mL, 15.789 mmol, 1.2 eq) into dry DCM (70 mL) was cooled to -78 ^oC under inert atmosphere. To this DMSO (2.23 mL, 31.56 mmol, 2.4 eq) was added dropwise at -78 ^oC over a period of 10 min followed by solution of compound 2-(benzyloxy)ethanol **288** (2.0 g, 13.150mmol, 1.0 eq) into dry DCM (30 mL) over a period of 20-25 min by maintaining temp below -70 ^oC. The resulting suspension was stirred at -78 ^oC for 30 min and quenched with TEA (9.15 mL, 65.750 mmol, 5.0 eq). The reaction mixture was brought to 20-21 ^oC and stirred for 30 min. The reaction mixture was diluted with diethyl ether and filtered through bed of $MgSO_4$. The filtrate was concentrated to give a yellow oil. The crude oil was filtered through a short silica gel column to

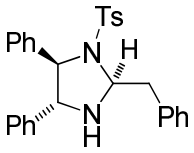
give compound 2-(benzyloxy)acetaldehyde **289** as yellowish oil (0.530 g, 3.533 mmol, 26%). The crude product was as such used for next step.

(4*R*,5*R*)-2-[(Benzyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine (283).



The procedure is same as for preparation of compound **(**4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **278**. During the reaction solid was not separated out. The reaction mixture was filtered, washed with methanol and filtrate was concentrated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (8:2) to give compound (4*R*,5*R*)-2-[(benzyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **283** as a colourless oil (1.1 g, 2.209 mmol, 73%). $[\alpha]_D^{15}$ = -44.9 (*c* 0.510 in $CHCl_3$); ν_{max} 1731, 1282, 1073, 968, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.55 (2H, d, *J* 8.4, *o*-C*H* of -SO_2PhCH_3), 7.31 (7H, m, *o*,*m*,*p*-C*H* of both Ph), 7.18 (8H, m, *o*,*m*,*p*-C*H* of -OCH_2Ph, -CH of both Ph), 6.92 (2H, dd, *J* 7.5, 1.5, *m*-C*H* of -SO_2PhCH_3), 5.04 (1H, m, -C*H*-CH_2OCH_2Ph), 4.67 (2H, dd, *J* 11.7, 5.4, -CH_2 of -OCH_2Ph), 4.58 (1H, d, *J* 6, -C*H*-NTs-), 4.28 (1H, d, *J* 6, -C*H*-NH-), 4.03 (1H, dd, *J* 6, 4.2, -CH_2-OCH_2Ph), 3.92 (1H, dd, *J* 6.9, 3.3, -CH_2-OCH_2Ph), 2.39 (3H, s, -SO_2PhCH_3), 2.17 (1H, s, -N*H*); δc (75 MHz, $CDCl_3$) 143.61, 140.03, 138.40, 137.94, 134.22, 129.52(2C), 128.55(2C), 128.46(2C), 128.33(2C), 127.91(2C), 127.81, 127.74(2C), 127.60, 127.49, 126.76(4C), 76.36, 73.65, 71.32, 70.86, 69.60, 21.55; m/z ESI-MS $[M+H]^+$ 499.5; HRMS found 499.2070 ($C_{30}H_{30}N_2O_3S$ H+ requires 499.2050, error = -4.0 ppm).

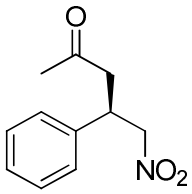
3.2.4 (4*R*,5*R*)-2-Benzyl-4,5-diphenyl-1-tosylimidazolidine (284).



The procedure is same as for preparation of compound **(**4*R*,5*R*)-2-[(*t*-butyldiphenylsilyloxy)methyl]-4,5-diphenyl-1-tosylimidazolidine **278** During the reaction a solid did not separate out. The reaction mixture was filtered, washed with methanol and the filtrate was concentrated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (8:2) to give compound (4*R*,5*R*)-2-benzyl-4,5-diphenyl-1-tosylimidazolidine **284** as yellowish solid (0.230 g, 0.491 mmol, 72%). Mp 68-70 ^{o}C; $[\alpha]_D^{24}$ = -14.4 (*c* 0.540 in $CHCl_3$); ν_{max} 3028, 291, 1599, 1494, 1453, 1343, 1160, 1090, 812, 746, 699, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.61 (2H, d, *J* 11.2, *o*-C*H* of -SO_2PhCH_3), 7.31 (5H, m, *o*,*m*,*p*-C*H* of both Ph), 7.19 (10H, m, *o*,*m*,*p*-C*H* of both Ph), 6.90 (2H, dd, *J* 9.6, 1.6, *m*-C*H* of -SO_2PhCH_3), 5.12 (1H, dd, *J* 12, 4, -C*H*-CH_2Ph), 4.54 (1H, d, *J* 8.8, -C*H*-NTs-), 4.29 (1H, d, *J* 8.83, -C*H*-NH-), 3.46 (1H, dd, *J* 18.4, 4, -CH_2Ph), 3.24 (1H, dd, *J* 18.4, 12.4, -CH_2Ph), 2.40 (3H, s, -SO_2PhCH_3), 2.29 (1H, br s, -N*H*); δc (75 MHz, $CDCl_3$) 143.67, 139.84, 138.14, 137.22, 134.27, 129.91(2C), 129.57(2C), 128.55(4C), 128.38(2C), 127.73(4C), 127.46, 126.78(2C), 126.52(2C), 78.98, 71.21, 69.64, 42.63, 21.56; m/z ESI-MS $[M+H]^+$ 469.1; HRMS found 469.1948 ($C_{29}H_{28}N_2O_2S$ H+ requires 469.1944, error = -0.9 ppm).

3.3 Use of synthesised derivatives as organocatalysts in asymmetric reactions

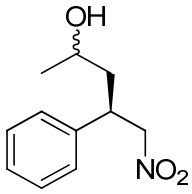
3.3.1 5-Nitro-4-phenylpentan-2-one (54).



This is a known compound.

To a test tube fitted with a magnetic stirrer was added *trans*-β-nitrostyrene (90.4 mg, 0.606 mmol, 1.0 eq), acetone (0.445 mL, 6.06 mmol, 10 eq) distilled water (21.8 µL, 1.21 mmol, 2 eq), glacial acetic acid (3.47 µL, 0.0606mmol, 0.1 eq), catalyst (10 mol%) and solvent (1.0 mL). The reaction mixture was stirred at ambient temperature for 17 h. The reaction was monitored by ^{1}H-NMR. The small fraction of reaction mixture was taken, filtered through a plug of silica, concentrated and taken for ^{1}H-NMR. After 5 days, the reaction mixture was concentrated on a rotavapor. The residue was purified by flash column chromatography to give compound 5-nitro-4-phenylpentan-2-one **54** as an off white solid (40 mg, 0.195 mmol, 32%). δ_H (300 MHz, $CDCl_3$) 7.21 (5H, m, -C_6H_5), 4.63 (1H, m, -C*H*HNO_2), 4.53 (1H, m, -CH*H*NO_2), 3.94 (1H, m, -C*H*C_6H_5), 2.84 (2H, d, *J* 6.9, -C*H*$_2$CO), 2.05 (3H, s, -C*H*$_3$). δc (75 MHz, $CDCl_3$) 138.82, 129.09(2C), 127.93, 127.39(2C), 79.46, 46.13, 39.04, 30.42 (The chiral HPLC method was already optimised in the group after reduction of the product[75]) The spectroscopic data were in agreement with literature values.[78]

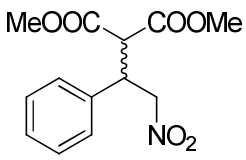
5-Nitro-4-phenylpentan-2-ol (268).



This is a known compound.[76]

To a solution of 5-nitro-4-phenylpentan-2-one **54** (35 mg, 0.169 mmol) in dichloromethane (0.25 mL) and methanol (0.25 mL) was added sodium borohydride (7 mg, 0.186 mmol, 1.1 eq) at ambient temperature. The reaction mixture was stirred for 1.5 h. The reaction mixture was quenched with 1M HCl (2 mL) and stirred for 5-8 min. The reaction mixture was extracted with dichloromethane (3 x 5 mL). The organic layer was separated, washed with distilled water (5 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give an oil. The oil was purified by flash column chromatography to give 5-nitro-4-phenylpentan-2-ol **268** as a colourless oil (15 mg, 0.071 mmol, 42%). ν_{max} 3375, 2968, 2932, 1560, 1495, 1455, 1432, 1378, 764, 700, 668 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.29 (5H, m, -C_6H_5), 4.62 (2H, m, -CH_2NO_2), 3.64 (2H, m, -CH_2), 1.95 (1H, m, -C*H*), 1.78 (1H, d, *J* 6.9, -C*H*OH), 1.58 (1H, br s, -O*H*), 1.16 (3H, m, -CH_3); m/z ESI-MS $[M+Na]^+$ 232.0; The enantiomeric excess was obtained by HPLC analysis (ChiralPak IB Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50 mL/min, 210 nM, 17 ^oC). Method previously developed: separation achieved on IB column with best separation on more polar isomer (HPLC conditions: Chiralpak IB, 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50 mL/min, 210 nm uv detection, 17 ^oC; 'fast' diastereoisomer by flash chromatography; 43.8 min (overlapping, no separation), 'slow'isomer; 56.7 min (Major from *R* ketone), 65.3 min (minor from *S* ketone). The spectroscopic data were in agreement with literature values.[76]

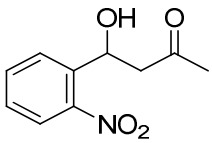
3.3.2 Methyl 2-carbomethoxy-4-nitro-3-phenylbutyrate (72).



This is a known compound.[66]

To a solution of *trans*-β-nitrostyrene (0.100 g, 0.670 mmol) and catalyst (10 mol%) in dry toluene (2 mL) was added dimethyl malonate (0.153 mL, 1.340 mmol, 2.0 eq). The resulting mixture was stirred at ambient temperature for 21 h. The reaction was monitored by ^{1}H-NMR. The small fraction of reaction mixture was taken, filtered through a plug of silica, concentrated and taken for ^{1}H-NMR. On ^{1}H-NMR there was only 9% conversion, the reaction mixture was stirred for 2 days and again checked as mentioned above. There was only 27% conversion to the required compound methyl 2-carbomethoxy-4-nitro-3-phenylbutyrate **72**. ν_{max} 2956, 1732, 1550, 1497, 1455, 1434, 1379, 1152, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.37 (3H, m, *m,p*-C*H* of Ph), 7.22 (2H, m, *o*-C*H* of both Ph), 4.87 (2H, m, -C*H*$_2$NO$_2$), 4.24 (1H, q, *J* 6.9, -C*H*-C$_6$H$_5$), 3.86 (1H, d, J 9, -C*H*(COOCH$_3$)$_2$), 3.76 (3H, s, -COOC*H*$_3$), 3.56 (3H, s, -COOC*H*$_3$); δc (75 MHz, $CDCl_3$) 167.85, 167.25, 136.12, 129.04(2C), 128.44, 127.86(2C), 77.47, 54.75, 53.03, 52.85, 42.93; m/z ESI-MS $[M+H]^+$ 282.1; The enantiomeric excess was obtained by HPLC analysis (ChiralPak AD Column: 0.46 cm x 25 cm, hexane:IPA 70:30, 0.50 mL/min, 210 nM, 15 ^{o}C) R_t (min) = 11.13 (minor enantiomer, *R*), 15.36 min (major enantiomer, *S*). The spectroscopic data were in agreement with literature values. [66]

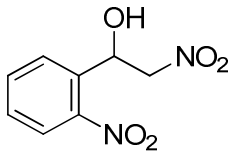
3.3.3 4-Hydroxy-4-(2-nitrophenyl)butan-2-one (80).



To a catalyst (10 mol%) and/or metal complex (10 mol%) in acetone (0.270 mL) was added 2-nitro benzaldehyde (25 mg, 0.166 mmol, 1 eq). The resulting mixture was

stirred at 20-21 ^{o}C and monitored by TLC. For slower reaction, ^{1}H-NMR was done after 5 days to give % conversion. The reaction mixture was concentrated and crude residue was purified by column chromatography to give 4-hydroxy-4-(2-nitrophenyl)butan-2-one **80**. The pure compound obtained was analysed by ^{1}H-NMR and chiral HPLC. δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.96 (1H, dd, *J* 9.6, 1.2, -C*H* of Ph), 7.89 (1H, dd, *J* 7.8, 1.2, -C*H* of Ph), 7.66 (1H, dt, *J* 7.6, 1.2, -C*H* of Ph), 7.44 (1H, dt, *J* 7.8, 1.5, -C*H* of Ph), 5.67 (1H, td, *J* 9.3, 2.1, -C*H*OH), 3.75 (1H, d, *J* 3.0, -O*H*), 3.14 (1H, dd, *J* 18.0, 2.1, -CH_2), 2.72(1H, dd, *J* 17.7, 9.3, -CH_2), 2.24 (3H, s, CH_3); The enantiomeric excess was obtained by HPLC analysis (ChiralPak IB Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50 mL/min, 210 nM, 18 ^{o}C) R_t (min) = 33.58 (minor enantiomer), 35.83 min (major enantiomer). The spectroscopic data were in agreement with literature values.[40,95]

3.3.4 2-Nitro-1-(2-nitrophenyl)ethanol (98).

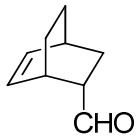


This is a known compound.[100-101]

A solution of metal complex (10 mol%) and catalyst (10 mol%) in dry ethanol (0.7 mL) was stirred at 20-21 ^{o}C for 1-1.5 h. To this, 2-nitro benzaldehyde (25 mg, 0.166 mmol, 1 eq) was added followed by nitromethane (90 µL, 1.660 mmol, 10 eq). The resulting mixture was stirred at 20-21 ^{o}C and monitored by TLC. For slower reactions, ^{1}H-NMR was done after 4 days to obtain % conversions. The reaction mixture was concentrated and crude residue was purified by column chromatography to give 2-nitro-1-(2-nitrophenyl)ethanol **98**. ν_{max} 3532, 2919, 1633, 1550, 1520,

1494, 1454, 1417, 1377, 1343, 1065, 762, 697cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.37 (4H, m, -C_6H_4), 5.47 (1H, dd, *J* 6.3, 2.4, -C*H*OH), 4.66 (2H, m, -CH_2NO_2), 2.94 (1H, br s, -O*H*); δc (75 MHz, $CDCl_3$) 146.58, 133.81, 133.39, 129.09, 128.09, 124.42, 79.44, 66.16; m/z ESI-MS $[M+H]^+$ 212.1; The enantiomeric excess was obtained by HPLC analysis (ChiralPak IB Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50 mL/min, 210 nM, 18 ^oC) R_t (min) = 31 (major enantiomer, *R*), 34 min (minor enantiomer, *S*).The spectroscopic data were in agreement with literature values.[100-101]

3.3.5 Bicyclo[2.2.2.]oct-5-ene-2-carboxaldehyde (293a/293b).



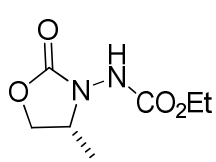
This is a known compound.[51,240]

To a mixture of catalyst (42.7 mg, .0624 mmol, 0.1 eq) in CH_3CN:H_2O (1 mL, 95:5) was added acrolein (0.125 mL, 1.872 mmol, 3.0 eq) and resulting solution was stirred for 5 min. To this, 1,3-cyclohexadiene (69.5 µL, 0.824 mmol, 1.0 eq) was added. The resulting mixture was stirred at 19-20 ^oC for 24h. The completion of the reaction was checked by ^{1}H-MNR. The reaction mixture was diluted with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to give mixture of compound *endo* **293a** and *exo* **293b** as crude oil. A crude ^{1}H-NMR spectrum at this point was used to determine the *endo*:*exo* ratio (known compounds). The crude product was purified by column chromatography using hexane:EtOAc (92:8) to give endo compound bicyclo[2.2.2.]oct-5-ene-2-carboxaldehyde **293a** as an oil (35 mg, 0.257

mmol, 41%). ν_{max} 3046, 2940, 2868, 1787, 1700, 1413, 1317, 1236, 1206, 1173, 1049, 984, 949, 904, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 9.43 (1H, d, *J* 1.5, -C*H*O), 6.31 (1H, t, *J* 7.5, -C*H*=CH), 6.09 (1H, t, *J* 7.5, -CH=C*H*), 2.93 (1H, m, -C*H*H-CHCHO), 2.62 (1H, m, -CH*H*-CHCHO), 2.54 (1H, m, -C*H*CHO), 1.68 (3H, m, -C*H* and -CH_2), 1.53-1.48 (1H, m, -C*H*), 1.38-1.19 (2H, m, -CH_2); δc (75 MHz, $CDCl_3$) 164.05, 134.75, 130.73, 41.93, 31.74, 28.95, 28.67, 24.71, 23.68; m/z ESI-MS $[M+Na]^+$ 169;. The enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 115 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Helium) R_t (min) = 43.14 (minor enantiomer), 43.64 min (major enantiomer), %ee = 72%. The spectroscopic data were in agreement with literature values.[51,240]

The sample of aldehyde formed **293a** was reduced to the corresponding alcohol using $NaBH_4$ and shown by optical rotation to be of *S*- configuration; $[\alpha]_D^{28}$ = -13.33 (*c* 0.06 in EtOH), 72% ee, *S*- enantiomer, [Literature values reported for this compound show a wide variation however in all cases the *S*- enantiomer has a negative sign: Lit. value 1;[240b] $[\alpha]_D^{28}$ = +5.36 (c=1.5, EtOH), 100% ee *R*-enantiomer, Lit. value 2;[240c] $[\alpha]_D^{25}$ = +8.4 (c=2.7, EtOH), 71% ee *R*- enantiomer, Lit. value 3;[240d] $[\alpha]_D^{28}$ = -10.2 (c=0.94, EtOH), 99% ee *S*- enantiomer].

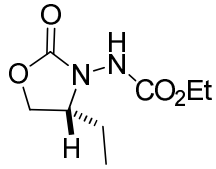
3.3.6 (*R*)-3-Ethoxycarbonylamino-4-methyl-2-oxazolidinone (109a).



This is a known compound.[116]

To a catalyst (10 mol%) was added propionaldehyde **107a** (0.110 mL, 1.50 mmol, 1.5 eq) followed by DEAD (0.164 mL, 1.0 mmol, 1.0 eq). The resulting mixture was stirred at ambient temperature to give colourless solution from yellow (colour of diethyl azodicarboxylate) (100% conversion). The reaction mixture was diluted with MeOH (2.5 mL) followed by careful addition of $NaBH_4$ (50 mg, 1.321 mmol, 1.321 eq) and mixture was stirred for 30 min. To this 0.5 N NaOH solution (2.5 mL) was added and stirred at ambient temperature for 2.5 h. The reaction mixture was concentrated on a rotavapor, diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give residue. The crude compound was purified by flash column chromatography using hexane:EtOAc 20:80 to give compound **(***R*)-3-ethoxycarbonylamino-4-methyl-2-oxazolidinone **109a** as a colourless oil (0.104 g, 0.553 mmol, 55%). $[\alpha]_D^{28}$ = -19.85 (*c* 1.4 in $CHCl_3$) [Lit. value $[\alpha]_D^{28}$ = -19.4 (*c* = 1.7g/100 mL $CHCl_3$)] ; ν_{max} 3284, 2982, 1769, 1721, 1512, 1480, 1416, 1383, 1200, 1114, 1042, 976, 781, 758, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 6.60 (1H, br s, -N*H*), 4.50 (1H, t, *J* 8.2, -OC*H*H-CH-), 4.23 (2H, q, *J* 6.9, -OC$H_2$$CH_3$), 4.09 (1H, br s, -C*H*), 3.91 (1H, t, *J* 8.7, -OC*H*H-CH-), 1.33-1.27 (6H, m, -CHCH_3 and -OCH_2CH_3); δc (75 MHz, $CDCl_3$) 68.19, 61.89, 52.24, 16.26, 13.73; m/z ESI-MS $[M+H]^+$ 189, $[M+Na]^+$ 211; The enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 150 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Helium) R_t (min) = 170.07 min (major enantiomer, *R*), 172.02 min (minor enantiomer, *S*), %ee = 95%. The spectroscopic data were in agreement with literature values.[116]

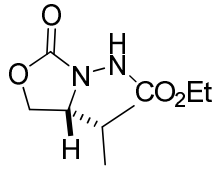
(*R*)- 4-Ethyl-3-ethoxycarbonylamino-2-oxazolidinone (109b).



This is a known compound.[116] The procedure is same as for preparation of compound **(***R*)-3-ethoxycarbonylamino-4-methyl-2-oxazolidinone **109a**.

$[\alpha]_D^{28}$ = -34.6 (*c* 0.4 in $CHCl_3$) [Lit. value $[\alpha]_D^{28}$ = -25.5 (*c* = 1.66g/100 mL $CHCl_3$)]; ν_{max} 3289, 2971, 2937, 1767, 1713, 1512, 1423, 1377, 1300,1215, 1121, 1049, 1014, 760, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 6.96-6.64 (1H, brs, -N*H*), 4.49 (1H, m, -NC*H*), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.01(2H, m, OCH_2-CH-), 1.84 (1H, m, -CH-C*H*H-CH_3), 1.59 (1H, m, -CH-CH*H*-CH_3), 1.29 (3H, t, *J* 7.6, OCH_2CH_3), 0.93 (3H, t, *J* 7.6, -CH_2CH_3); δc (75 MHz, $CDCl_3$) 67.08, 62.45, 57.59, 24.31, 14.31, 8.41; m/z ESI-MS $[M+H]^+$ 203, $[M+Na]^+$ 225; The enantiomeric excesses were determined by Chiral GC (Chrompak CP-ChirasilDex Cβ Column, Oven temperature 150 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Helium) R_t (min) = 144.7 min (minor enantiomer, *S*), 149.1 min (major enantiomer, *R*), %ee = 97%. The spectroscopic data were in agreement with literature value.[116]

(*R*)-3-Ethoxycarbonylamino-4-isopropyl-2-oxazolidinone (109c).

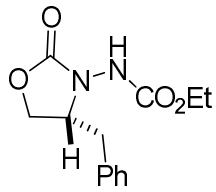


This is a known compound.[116] The procedure is same as for preparation of compound **(***R*)-3-ethoxycarbonylamino-4-methyl-2-oxazolidinone **109a**.

$[\alpha]_D^{28}$ = -21.29 (*c* 0.425 in $CHCl_3$) [Lit. value $[\alpha]_D^{28}$ = -18.6 (*c* = 1.25g/100 mL $CHCl_3$)]; ν_{max} 3285, 2965, 1770, 1716, 1512, 1482, 1371, 1297, 1215, 1118, 1050, 764, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 6.69-6.47 (1H, br s, -N*H*), 4.39 (1H, t, *J*

8.7, -OC*H*H-CH-), 4.21 (2H, q, *J* 5.4, -OC*H*$_2$CH$_3$), 4.08 (1H, t, *J* 8.8, -OCH*H*-CH-), 3.97 (1H, br s, -OCH$_2$-C*H*), 2.00 (1H, m, -C*H*(CH$_3$)$_2$), 1.27 (3H, t, *J* 5.4, -OCH$_2$C*H*$_3$), 0.93 (3H, d, *J* 7.05, CH(C*H*$_3$)$_2$), 0.94 (3H, d, *J* 7.2, -CH$_3$ of -CH(C*H*$_3$)$_2$); δc (75 MHz, CDCl$_3$) 63.97, 62.44 60.74, 28.430, 17.76, 15.78, 14.31; m/z ESI-MS $[M+H]^+$ 217, $[M+Na]^+$ 239; The enantiomeric excess was obtained by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 180 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Helium) R_t (min) = 72.16 min (minor enantiomer, *S*), 75.50 min (major enantiomer, *R*), %ee = 96%. The spectroscopic data were in agreement with literature values. [116]

(*R*)-4-Benzyl-3-ethoxycarbonylamino-2-oxazolidinone (109d).



This is a known compound.[116] The procedure is same as for preparation of compound **(*R*)**-3-ethoxycarbonylamino-4-methyl-2-oxazolidinone **109a**.

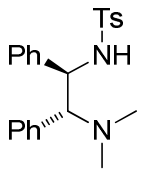
$[\alpha]_D^{28}$ = -29 (*c* 0.490 in CHCl$_3$) [Lit. value $[\alpha]_D^{28}$ = -30.6 (*c* = 1.78g/100 mL CHCl$_3$)]; ν_{max} 3289, 2967, 1780, 1722, 1505, 1210, 1115, 1050, 751, 709 cm^{-1}; δ_H (300 MHz, CDCl$_3$, Me$_4$Si) 7.34-7.28 (3H, m, -Ph), 7.20-7.10 (2H, m, -Ph), 6.66-6.46 (1H, br s, -NH), 4.38-4.32 (2H, m, -CH$_2$OCO), 4.24-4.20 (2H, m, -OC*H*$_2$CH$_3$), 4.08-4.00 (1H, m, -NCH), 3.17 (1H, dd, *J* 13.6, 3.6, -C*H*H-Ph), 2.80 (1H, dd, *J* 13.6, 8.4, --CH*H*-Ph), 1.28 (3H, t, *J* 7.2, -OCH$_2$C*H*$_3$); δc (75 MHz, CDCl$_3$) 135.12, 128.55(2C), 128.90(2C), 127.23, 67.06, 62.52, 57.69, 37.94, 14.32; m/z ESI-MS $[M+Na]^+$ 287; The spectroscopic data were in agreement with literature values. [116]

The alcohol was prepared by $NaBH_4$ reduction of the initial addition product without subsequent cyclisation and isolated in crude form for analysis to avoid inadvertent enrichment of the ee: δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.25 (5H, m, -Ph), 6.35 (1H, brs, N*H*), 4.70-4.50 (1H, O*H*, two rotamers), 4.25 (3H, br m, -C*H*, -CH_2), 4.05 (2H, br m, CH_2), 4.57-3.40 (2H, br m, CH_2), 2.61 (2H, br m, CH_2), 1.25 (3H, t, *J* 7.0, CH_3), 1.15 (3H, t, *J* 6.5,CH_3); δc (75 MHz, $CDCl_3$) 137.3, 128.9, 128.8, 128.6, 128.5, 126.7, 63.0, 62.8, 62.0, 34.6, 14.3 (complicated by rotamers); m/z ESI-MS $[M+Na]^+$ 333; The enantiomeric excess (example in SI below)was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm3x 25 cm, hexane:IPA 90:10, 0.50mL/min, 216 nM, 15 ^oC) R_t (min) = 22.02 (minor enantiomer), 24.86 min (major enantiomer), %ee = 84%.

3.4 Synthesis of Ru complexes

3.4.1 Synthesis of *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzene ruthenium chloride (299).

***N*-[(1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide (300).**

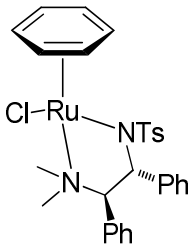


This is a known compound.[261]

To a solution of (*1R,2R*)-TsDPEN **64** (1.00 g, 2.73 mmol) in dry methanol (30 mL) was added 37% formaldehyde solution (1 mL, ~ 4.5 eq) and the mixture was stirred for 15 min at 21 ^oC under inert atmosphere. To this $NaBH_3CN$ (0.684 g, 10.88 mmol, 4.0 eq) was added slowly and the mixture was stirred for 15 min followed by

addition of acetic acid (2 mL, ~12.5 eq). The reaction mixture was heated to 50 ^{o}C and stirred for 18 h, then cooled to room temperature and diluted with 2% MeOH in DCM (100 mL). The mixture was washed with 1M NaOH (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed on a rotavapor to give compound *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **300** as white solid (1.08 g, 2.741 mmol, 100%). Mp 102-104 ^{o}C; $[\alpha]_D^{24}$ = +54.9 (*c* 0.570 in $CHCl_3$); ν_{max} 1452, 1366, 1310, 1147, 1095, 1050, 937, 814, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.4, *o*-CH of -$SO_2C_6H_4CH_3$), 7.16 (3H, m, ArH), 7.07 (2H, d, *J* 8.1, *m*-CH of -$SO_2C_6H_4CH_3$), 6.92 (7H, m, ArH), 6.81 (1H, br s, -N*H*Ts), 4.61 (1H, d, *J* 11.1, -C*H*NHTs), 3.54 (1H, d, *J* 10.8, -C*H*N$(CH_3)_2$), 2.33 (3H, s, -CH_3), 2.06 (6H, s, -N(CH_3)$_2$); δc (75 MHz, CDCl3) 142.61, 137.95, 137.04, 130.89, 129.72(2C), 128.87(2C), 128.32(2C), 127.59(2C), 127.52(2C), 127.23(2C), 126.94(2C), 73.33, 57.21, 40.06(2C), 21.34; m/z ESI-MS $[M+H]^+$ 395.2; HRMS found 395.1791 ($C_{23}H_{26}N_2O_2S$ H+ requires 395.1788, error = -1.1 ppm).

_N_-[(1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzeneruthenium chloride (299).



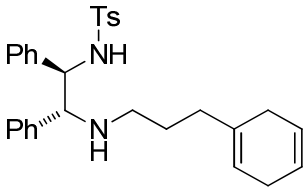
This is a novel compound.

A mixture of *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **300** (0.250 g, 0.635 mmol), benzeneruthenium (II)

chloride dimer (0.318 g, 0.635 mmol, 1.0 eq) and triethylamine (0.353 mL, 2.54 mmol, 4.0 eq) in IPA (25 mL) was heated at 80 ^{o}C for 1 h under an inert atmosphere. The reaction mixture was cooled to room temperature and concentrated to give a residue. The residue was filtered and washed with water to leave a solid. The solid was purified by flash column chromatography on Florisil. The complex was eluted in Hexane:EtOAc:MeOH (5:4:1) to give compound *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzeneruthenium chloride **299** as light brown solid (0.145 g, 0.238 mmol, 38%). Mp 146-148 ^{o}C with decomposition; $[\alpha]_D^{20}$ = +1687 (*c* 0.0048 in $CHCl_3$); ν_{max} 2921, 1452, 1437, 1252, 1129, 1086, 942, 809, 699, 663 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.1, *o*-CH of -$SO_2C_6H_4CH_3$), 7.13 (2H, m, ArH), 6.96 (4H, m, ArH), 6.80 (2H, d, *J* 7.8, *m*-CH of -$SO_2C_6H_4CH_3$), 6.58 (4H, m, ArH), 5.79 (6H, s, -C_6H_6), 4.90 (1H, d, *J* 11.7, -C*H*NHTs), 4.58 (1H, d, *J* 11.7, -C*H*N$(CH_3)_2$), 3.20 (3H, s, -N(C*H*$_3)_2$), 2.89 (3H, s, -N(C*H*$_3)_2$), 2.20 (3H, s, -C*H*$_3$); δc (75 MHz, $CDCl_3$) 142.27, 139.65, 139.19, 130.11(2C), 129.65, 128.96, 128.56, 128.37, 128.10(2C), 127.67, 127.60, 126.80(2C), 126.33(2C), 125,46, 84.46(6C), 76.88, 66.38, 52.24, 50.15, 21.17; m/z ESI-MS $[M-Cl]^+$ 573.0; HRMS found 573.1147 ($C_{29}H_{31}ClN_2O_2RuS$-Cl requires 573.1147, error = 0.7 ppm); The X-ray Structure was obtained (more details in Appendix 5.1.2).

3.4.2 Synthesis of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer (302).

***N*-[(1*R*,2*R*)-2-(3-Cyclohexa-1,4-dienylpropylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide (179).**

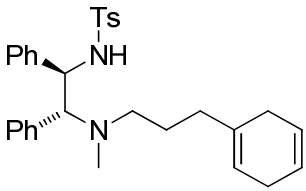


This is a known compound.[205]

To a solution of (*1R,2R*)-TsDPEN **64** (1.50 g, 4.09 mmol, 1.25 eq) in dry methanol (20 mL) was added a solution of aldehyde **304** (0.445 g, 3.27 mmol, 1.0 eq) in dry methanol (10 mL) and MS 4Å (1.5 g) followed by acetic acid (3-4 drops) at 21 ^{o}C under an inert atmosphere. The resulting suspension was stirred for 2.5 h to form an imine. To this, $NaBH_3CN$ (0. 4 g, 6.54 mmol, 2.0 eq) was added slowly and the resulting mixture was stirred for 48 h at 22 ^{o}C. The reaction mixture was filtered and concentrated to give residue. The residue was dissolved in DCM (50 mL) and washed with 1M NaOH (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated on a rotavapor to give white solid. The crude compound was purified by flash column chromatography using hexane:EtOAc (8:2) to give compound *N*-[(1*R*,2*R*)-2-(3-cyclohexa-1,4-dienylpropylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **179** as white solid (1.280 g, 2.633 mmol, 78%). Mp 106-108 ^{o}C; $[\alpha]_D^{24}$ = -10.35 (*c* 0.285 in $CHCl_3$); ν_{max} 3294, 2819, 1454, 1430, 1333, 1129, 1060, 806, 699, 684 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.1, *o*-CH of -$SO_2C_6H_4CH_3$), 7.13 (3H, m, ArH), 7.07 (5H, m, ArH), 6.90 (4H, m, ArH), 6.28 (1H, br s, -N*H*Ts), 5.68 (2H, m, -C*H*=C*H*), 5.30 (1H, m, -C*H*=C), 4.24 (1H, d, *J* 8.1, -C*H*NHTs), 3.60 (1H, d, *J* 7.8, -C*H*NH$(CH_2)_3$-), 2.64 (2H, m, -CH_2CH=CH-), 2.51 (2H, m,-CH_2CH_2CH_2NH-), 2.43-2.22 (2H, m, -CH_2 of -CH_2CH=CH), 2.33 (3H, s, -CH_3), 1.87 (2H, m, -NH-CH_2-), 1.70 (1H, br s, -N*H*$(CH_2)_3$-), 1.50 (2H, m, -CH_2C$H_2$$CH_2$); δc (75 MHz, $CDCl_3$) 142.63, 139.31, 138.35, 137.01, 134.25,

129.04(2C), 128.26(2C), 127.88(2C), 127.51(2C), 127.40, 127.33(2C), 127.23, 127.08(2C), 124.21(2C), 118.68, 67.75, 63.02, 46.64, 34.79, 29.77, 27.45, 26.70, 21.40; m/z ESI-MS $[M+H]^+$ 487.2; HRMS found 487.2427 ($C_{30}H_{34}N_2O_2S$ H+ requires 487.2414, error = -2.7 ppm). The spectroscopic data were in agreement with literature values.[205]

***N*-[(1*R*,2*R*)-2-((3-Cyclohexa-1,4-dienyl)propyl)(methyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide (305).**

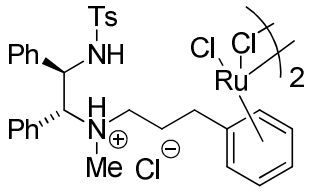


This is a novel compound.

To a solution of *N*-[(1*R*,2*R*)-2-(3-cyclohexa-1,4-dienylpropylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **179** (0.5 g, 1.03 mmol) in dry methanol (15 mL) was added 37% formaldehyde solution (0.251mL, ~ 3.0 eq) and the mixture was stirred for 15 min at 21 ^oC under an inert atmosphere. To this, $NaBH_3CN$ (0.129 g, 2.06 mmol, 2.0 eq) was added slowly and the mixture stirred for 15 min followed by addition of acetic acid (2-3 drops). The reaction was heated to 50 ^oC and stirred for 16 h, then cooled to room temperature and diluted with 2% MeOH in DCM (50 mL). The mixture was washed with 1M NaOH (3 x 40 mL), dried over anhydrous $MgSO_4$, filtered and evaporated on a rotavapor to give crude product. The crude product was purified by flash column chromatography using Hexane:EtOAc (8.8:1.2) to give compound *N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **305** as a colourless oil (0.375 g, 0.750 mmol, 73%). $[\alpha]_D^{24}$ = +56.5 (*c* 0.115 in $CHCl_3$);

ν_{max} 3663, 3028, 2927, 2818, 1599, 1453, 13112, 1151, 1092, 932, 809, 699, 663 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.1, *o*-CH of $-SO_2C_6H_4CH_3$), 7.16 (3H, m, ArH), 7.06 (2H, d, *J* 8.1, *m*-CH of $-SO_2C_6H_4CH_3$), 6.93 (7H, m, ArH), 6.80 (1H, br s, -N*H*Ts), 5.73 (2H, m, -C*H*=C*H*), 5.48 (1H, m, -C*H*=), 4.67 (1H, d, *J* 11.1, -C*H*NHTs), 3.62 (1H, d, *J* 10.8, -C*H*NH$(CH_2)_3$-), 2.70 (2H, m, -CH_2CH=CH), 2.63 (2H, m, -$NCH_2CH_2CH_2$), 2.33 (3H, s, -CH_3), 2.23 (2H, m, -CH_2CH=CH), 2.03 (3H, s, -NCH_3), 1.99 (2H, m, -NHCH_2), 1.61 (2H, m, $-CH_2$ of $-NCH_2CH_2CH_2$); δc (75 MHz, $CDCl_3$) 142.64, 138.13, 137.29, 134.41, 131.85, 129.74(2C), 128.94(2C), 128.40(2C), 127.72(2C), 127.65, 127.60(2C), 127.27(2C), 127.00, 124.28(2C), 118.69, 72.67, 57.22, 53.34, 36.04, 35.00, 29.00, 26.78, 25.50, 21.42; m/z ESI-MS $[M+H]^+$ 501.2; HRMS found 501.2575 ($C_{31}H_{36}N_2O_2S$ H+ requires 501.2570, error = -1.0 ppm).

{*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)ammonium chloride)]-4-methylbenzenesulfonamide}ruthenium chloride dimer (306).

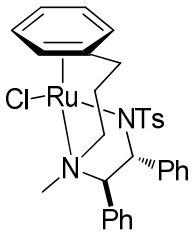


This is a novel compound.

To a solution of *N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **305** (0.355 g, 0.710 mmol) in DCM (10 mL) was added a 2M solution of HCl in diethyl ether (0.89 mL, 1.77 mmol) and the mixture was stirred at 22 ^oC for 30 min under an inert atmosphere. The solvents were removed under reduced pressure to give a residue. This was dissolved in ethanol (20 mL) and ruthenium trichloride trihydrate (0.139 g, 0.532

mmol) was added. The resulting mixture was heated at 78 ^{o}C for 16 h. The reaction mixture was cooled, solid separated out filtered and washed by ethanol to give compound {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)ammonium chloride)]-4 methylbenzenesulfonamide}ruthenium chloride dimer **306** as green solid (0.250 g, 0.177 mmol, 50%) which was used directly in the next step, m.p > 300 ^{o}C; m/z ESI-MS $[M\text{-}Cl]^{+}$ 599.1 (monomer formed by dimer cleavage and loss of HCl *in-situ*); ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 9.30-8.50 (2H, br s, NH), 7.60-6.80 (30H, m, ArH), 6.08-6.00 (4H, m, $\eta^{6}C_6H_5$), 5.95-5.80 (6H, m, $\eta^{6}C_6H_5$), 5.15-5.05 (2H, m, -CH), 4.95-4.80 (2H, m, -CH), 2.90-2.00 (12H, m, $-CH_2$), 2.40 (12H, brs, $-CH_3$).

{*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer (302).



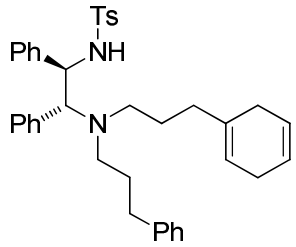
This is a novel compound.

A mixture of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)ammonium chloride)]-4-methylbenzenesulfonamide} ruthenium chloride dimer **306** (0.275 g, 0.195 mmol and triethylamine (0.162 mL, 1.168 mmol, 6.0 eq) in IPA (15 mL) was heated at 80 ^{o}C for 1 h under an inert atmosphere. The reaction mixture was cooled to room temperature and concentrated to give a residue. This was filtered and washed with water. The solid was purified by flash column chromatography on Florisil. The complex was eluted in

Hexane:EtOAc:MeOH (5:4:1) to give compound {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer **302** as a light brown solid (0.175 g, 0.276 mmol, 70%). Mp 184-186 ^{o}C with decomposition; $[\alpha]_D^{24}$ = +1394 (*c* 0.0052 in $CHCl_3$); ν_{max} 3435, 2973, 2924, 1600, 1454, 1267, 1129, 1085, 1045, 940, 841, 699, 664 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.44 (1H, br s, ArH), 7.28 (2H, d, *J* 7.6, ArH), 7.22 (1H, br s, ArH), 7.11 (1H, t, *J* 6.9, ArH), 6.97 (1H, br s, ArH), 6.89 (2H, br d, *J* 5.2, ArH), 6.73 (2H, d, *J* 7.6, *m*-CH of $-SO_2C_6H_4CH_3$), 6.60 (2H, m, ArH), 6.51 (2H, m, ArH), 6.44 (1H, t, *J* 4.9, *p*-CH of $\eta^6C_6H_5$), 6.29 (1H, d, *J* 4.4, *o*-CH of $\eta^6C_6H_5$), 5.74 (1H, t, *J* 5.3, *m*-CH of $\eta^6C_6H_5$), 5.46 (1H, t, *J* 5.2, *m*-CH of $\eta^6C_6H_5$), 5.31 (1H, d, *J* 5.6, *o*-CH of $\eta^6C_6H_5$), 4.87 (1H, d, *J* 12.0, -C*H*NHTs), 4.70 (1H, d, *J* 11.6, -C*H*N$(CH_2)_3$-), 3.31 (1H, t, *J* 11.8, -NCH_2), 2.93 (1H, br d, *J* 13.2, -NCH_2), 2.83 (3H, s, -NCH_3), 2.77 (1H, br d, *J* 9.2, $-NCH_2CH_2CH_2$), 2.39 (1H, m, $-NCH_2CH_2CH_2$), 2.29 (2H, m, $-NCH_2CH_2CH_2$), 2.17 (3H, s, -CH_3); δc (75 MHz, $CDCl_3$) 141.90, 139.52, 139.32, 134.40, 130.41, 130.12(2C), 129.86, 128.52, 128.14, 127.94(2C), 127.13, 126.74(2C), 126.24(2C), 125.20, 88.05, 87.12, 85.97, 85.05, 84.79, 84.59, 79.14, 66.42, 53.53, 48.40, 28.60, 23.77, 21.14; m/z ESI-MS $[M-Cl]^+$ 599.1; HRMS found 599.1314 ($C_{31}H_{33}ClN_2O_2RuS$-Cl requires 599.1308, error = -1.0 ppm); The X-ray Structure was obtained (more details in Appendix 5.1.3).

3.4.3 Synthesis of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer (303).

_N_-[(1*R*,2*R*)-2-((3-Cyclohexa-1,4-dienyl)propyl)(3-phenylpropyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide (308).

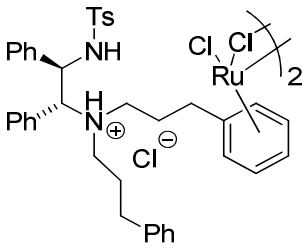


This is a novel compound.

To a solution of *N*-[(1*R*,2*R*)-2-(3-cyclohexa-1,4-dienylpropylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **179** (0.275 g, 0.566 mmol, 1.0 eq) in dry methanol (24 mL) was added phenyl propionaldehyde **307** (75 µL, 0.566 mmol, 1.0 eq) followed by acetic acid (3-4 drops) at 21 ^{o}C under inert atmosphere. The resulting suspension was stirred for 2.5 h to form the imine. To this, $NaBH_3CN$ (71.1 mg, 1.132 mmol, 2.0 eq) was added and resulting mixture was stirred at 50 ^{o}C for 22h. The reaction mixture was filtered and concentrated to give a residue. This was dissolved in DCM (20 mL) and washed with 1M NaOH (2 x 15 mL), dried over anhydrous $MgSO_4$, filtered and evaporated on a rotavapor to give the crude product which was purified by flash column chromatography using hexane:EtOAc (8.5:1.5) to give compound *N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(3-phenylpropyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **308** as an oil (0.190 g, 0.314 mmol, 55%). $[\alpha]_D^{24}$ = +18.54 (*c* 0.240 in $CHCl_3$); ν_{max} 3676, 2972, 1600, 1453, 1347, 1151, 1076, 1057, 932, 810, 699, 663 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.4, ArH), 7.13 (2H, m, ArH), 7.22-7.13 (6H, m, ArH), 7.02 (2H, d, *J* 8.1, *m*-CH of $-SO_2C_6H_4CH_3$), 6.90 (7H, m, ArH), 6.81 (1H, br s, -N*H*Ts), 5.72 (2H, m, -C*H*=C*H*), 5.45 (1H, m, -C*H*=), 4.74 (1H, d, *J* 10.8, -C*H*NHTs), 3.71 (1H, d, *J* 7.8, -C*H*NCH_2), 2.79-2.47 (8H, m, -CH_2), 2.31 (3H, s, -CH_3), 2.16-1.81 (6H, m, -CH_2), 1.62 (2H, m, -CH_2); δc (75 MHz, $CDCl_3$) 142.54, 141.86, 138.15, 137.51, 134.36, 133.05, 129.70(2C), 129.86(2C), 128.38(5C), 127.82(2C), 127.63,

127.58(2C), 127.19(2C), 126.98, 125.86(2C), 124.27(2C), 118.64, 69.31, 57.33, 49.11, 48.96, 35.12, 33.67, 30.06, 29.03, 26.75, 25.99, 21.39; m/z ESI-MS $[M+H]^+$ 605.3; HRMS found 605.3203 ($C_{39}H_{44}N_2O_2S$ H+ requires 605.3196, error = -1.0 ppm).

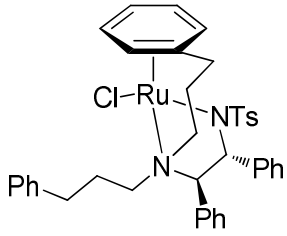
{*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)ammonium chloride]-4-methylbenzenesulfonamide}ruthenium chloride (309).



This is a novel compound.

To a solution of *N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(3-phenylpropyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **308** (0.175 g, 0.290 mmol) in DCM (10 mL) was added a 2M solution of HCl in diethyl ether (0.44 mL, 0.869 mmol) and the mixture was stirred at 22 ^oC for 30 min under an inert atmosphere. The solvents were removed under reduced pressure to give a residue. The residue was dissolved in ethanol (15 mL) and ruthenium trichloride trihydrate (61 mg, 0.232 mmol) was added. The resulting mixture was heated at 78 ^oC for 16 h. The reaction mixture was cooled, a solid separated out filtered and was washed by ethanol to give compound {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)ammonium chloride]-4-methylbenzenesulfonamide}ruthenium chloride dimer **309** as green solid (0.150 g, 0.097 mmol, 67%), Mp > 300 ^oC; m/z ESI-MS $[M-Cl]^+$ 703.1 (monomer formed *in-situ*). This was used directly in the next step.

{*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer (303).



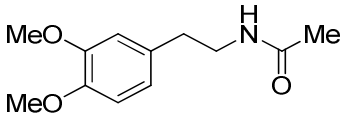
This is a novel compound.

A mixture of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)ammonium chloride]-4-methylbenzenesulfonamide}ruthenium chloride dimer **309** (0.100 g, 0.062 mmol and triethylamine (51.5 µL, 0.370 mmol, 6.0 eq) in IPA (10 mL) was heated at 80 ^{o}C for 1 h under inert atmosphere. The reaction mixture was cooled to room temperature and concentrated to give a residue. This was filtered and washed with water. The solid was purified by flash column chromatography on Florisil. The complex was eluted in Hexane:EtOAc:MeOH (5:4:1) to give compound {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(3-phenylpropyl)amino]-4-methylbenzenesulfonamide}ruthenium chloride monomer **303** as light brown solid (45 mg, 0.061 mmol, 49%). Mp 156-158 ^{o}C with decomposition; $[\alpha]_D^{24}$ = +1525 (*c* 0.004 in $CHCl_3$); ν_{max} 2972, 1600, 1494, 1453, 1259, 1131, 1086, 939, 842, 699, 664 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41 (1H, br d, ArH), 7.28-7.09 (7H, m, ArH), 6.95 (3H, m, ArH), 6.82 (2H, m, ArH), 6.70 (2H, d, *J* 8.1, *m*-CH of $-SO_2C_6H_4CH_3$), 6.57 (2H, m, ArH), 6.48 (2H, m, ArH), 6.37 (1H, d, *J* 5.19, *o*-CH of Ru-Ph), 6.32 (1H, t, *J* 5.7, *o*-CH of Ru-Ph), 5.74 (1H, t, *J* 5.8, *m*-CH of Ru-Ph), 5.36 (1H, t, *J* 5.8, *m*-CH of Ru-Ph), 4.79 (1H, d, *J* 6, -C*H*NHTs), 4.73 (2H, m, -C*H*N(CH_2), *p*-CH of Ru-Ph), 3.58 (1H, dt, *J* 13.6, 3.9, -N(C*H*$_2$)), 3.46-3.23 (3H, m, -N(C*H*$_2$)), 2.78 (1H, m, -C*H*$_2$), 2.30-2.20 (4H, m, -C*H*$_2$), 2.16 (3H, s, -C*H*$_3$),

2.15 (1H, m, -CH_2), 1.50 (1H, m, -CH_2), 1.03 (1H, m, -CH_2); δc (75 MHz, $CDCl_3$) 141.68, 140.90, 139.60, 139.12, 134.09, 132.89, 130.18(2C), 128.90, 128.72, 128.44(3C), 128.38(2C), 127.91(2C), 127.43, 126.84(2C), 126.26, 126.15(2C), 125.08, 86.93, 86.82, 86.68, 85.92, 85.62, 83.70, 78.25, 68.09, 60.82, 49.73, 33.04, 28.52, 26.79, 24.15, 21.14; m/z ESI-MS $[M-Cl]^+$ 703.1; HRMS found 703.1946 ($C_{39}H_{41}ClN_2O_2RuS$-Cl requires 703.1937, error = -1.3 ppm).

3.5 Synthesis of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (165).

***N*-(3,4-Dimethoxyphenethyl)acetamide.**

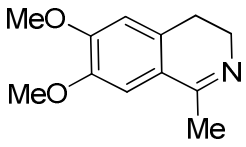


This is a known compound.[262]

To a solution of 3,4-dimethoxyphenethylamine (5.0 g, 27.624 mmol) in dry DCM (50 mL) was added acetic anhydride (2.61 mL, 27.6 mmol) at 18 ^oC under an inert atmosphere. The reaction mixture was stirred at 18-20 ^oC for 18 h. The reaction mixture was washed with saturated citric acid (10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and evaporated on a rotavapor to give a solid. The solid was scratched in hexane, filtered and dried to give compound *N*-(3,4-dimethoxyphenethyl)acetamide as a light brown solid (6.10 g, 27.354 mmol, 99%) Mp 100-102 ^oC; ν_{max} =3250, 3084, 2926, 2840, 1631, 1563, 1515, 1471, 1261, 1250, 1155, 1138, 1019, 814, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 6.85-6.73 (1H, m, ArH), 6.72-6.68 (2H, m, ArH), 5.58 (1H, br s, -N*H*), 3.87 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 3.54-3.46 (2H, m, -CH_2NHCO), 2.76 (2H, t, *J* = 6.9 Hz, -CH_2), 1.94 (3H, s, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 170.10, 147.68, 131.34, 120.60, 111.86, 111.34, 55.91,

55.87, 40.77, 35.18, 23.33; m/z ESI-MS $[M+H]^+$ 224, $[M+Na]^+$ 246. The spectroscopic data were in agreement with literature values.[262]

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (165).



This is a known compound.[262]

To a solution of *N*-(3,4-dimethoxyphenethyl)acetamide (6.0 g, 26.90 mmol) in dry toluene (50 mL) was added $POCl_3$ (2.50 mL, 26.90 mmol) at 20 ^oC under an inert atmosphere. The resulting mixture was refluxed at 111 ^oC for 2 h. The reaction mixture was cooled to room temperature and concentrated on a rotavapor to give a brown solid. The solid was dissolved in DCM (70 mL) was washed with saturated K_2CO_3 (2 x 25 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated on a rotavapor to give a solid. The solid was scratched in cold diethyl ether, filtered and dried to give compound 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **165** as light yellow solid (4.60 g, 22.439 mmol, 95%). Mp 124-126 ^oC; ν_{max} 2925, 1626, 1603, 1571, 1513, 1329, 1271, 1212, 1155, 1060, 871, 808 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.99 (1H, s, -C*H* of Ar), 6.69 (1H, m, -C*H* of Ar), 3.92 (3H, s, -OCH_3), 3.91 (3H, s, -OCH_3), 3.63 (2H, t, *J* 7.5, -CH_2N), 2.63 (2H, t, *J* 7.5, -CH_2), 2.36 (3H, s, -CH_3); δc (75 MHz, $CDCl_3$) 163.54, 150.73, 147.36, 131.05, 122.43, 110.15, 108.92, 56.14, 55.89, 46.97, 25.68, 23.39; m/z ESI-MS $[M+H]^+$ 206. The spectroscopic data were in agreement with literature values. [262]

3.5 Use of synthesised Ru complexes in pressure hydrogenation and transfer hydrogenation

3.5.1 Pressure hydrogenation:

A mixture of imine/ketone (50 mg) and catalyst (1 mol%) in solvent (0.5 mL) was stirred under H_2 (30 bar) at 30 ^oC for 18-22 h. An aliquot of the reaction mixture was filtered through a plug of silica and analysed by chiral GC for % conversion and ee.

With additive

A mixture of imine/ketone (50 mg), catalyst (1 mol%) and $AgSbF_6$ (4 mol%) in solvent (0.5 mL) was stirred under H_2 (30 bar) at 30 ^oC for 18-22 h. An aliquot of the reaction mixture was filtered through a plug of silica and analysed by chiral GC for % conversion and ee.

3.6.2 Asymmetric transfer Hydrogenation:

Without solvent:

A mixture of imine/ketone (50 mg), catalyst (1 mol%) in FA:TEA (5:2) (0.2 mL) was stirred at 30 ^oC for 18-22 h under inert atmosphere. For reaction monitoring, a aliquot of the reaction mixture was filtered through a plug of silica and analysed by chiral GC for % conversion and ee.

In solvent

A mixture of imine/ketone (50 mg), catalyst (1 mol%) and FA:TEA (5:2) (0.2 mL) in solvent (0.4 mL) was stirred at 30 ^oC for 18-22 h under an inert atmosphere. For reaction monitoring, an aliquot of the reaction mixture was filtered through a plug of silica and analysed by chiral GC for %conversion and ee.

3.6.3 400MHz NMR Kinetic study for reduction of ketone and imine:

Asymmetric transfer hydrogenation of acetophenone 112:

To a 5 mm NMR tube were added the catalyst (0.01 mmol), and formic acid/triethylamine 5:2 complex (1 mL). After 30 minutes acetophenone was added (120 mg, 1 mmol) followed by 0.05 mL of C_6D_6 hence providing a substrate solution of initially ca. 0.86M. The reaction was followed by ^{1}H-NMR until the specified conversion was achieved. The conversion was calculated by the integration of the methyl peak from the starting material at 2.44 ppm and the CH from the product at 4.77 ppm. At the end of the reaction the reaction mixture was flushed through a short pad of silica using EtOAc to elute. The alcohol was isolated by flash chromatography on silica gel and its ee was determined by chiral GC.[202]

Asymmetric transfer hydrogenation of Imine165:

To a 5 mm NMR tube were added the catalyst (0.005 mmol), and formic acid/triethylamine 5:2 complex (0.25 mL). After 30 minutes a solution of imine (0.5 mmol) in acetonitrile (0.8 mL) was added followed by 0.05 mL of C_6D_6 hence providing a substrate solution of initially ca. 0.45M. The reaction was followed by ^{1}H-NMR until complete reduction was observed. The conversion was calculated by the integration of the aromatic proton peak from the starting material as two singlets at 6.99, 6.69 ppm and the product at 6.50, 6.40 ppm. At the end of the reaction the reaction mixture was flushed through a short pad of silica using EtOAc to elute. The amine product was isolated by flash chromatography on silica gel and its ee was determined by chiral GC.[202]

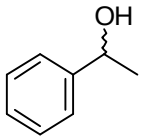
3.6.4 700 MHz NMR reactions for the asymmetric transfer hydrogenation of imine 165.

To a 5 mm NMR tube were added the imine (0.731 mmol), catalyst **299**/**302** (1/3 mol%), and formic acid/triethylamine 5:2 complex (0.6 mL) followed by 0.05 mL of C_6D_6. The reaction was followed by ^{1}H-NMR with hydride detection until complete reduction was observed. The conversion was calculated by the integration of the aromatic proton peak from the starting material as two singlets at 6.99, 6.69 ppm and the product (quite close two singlet) at 6.50, 6.40 ppm. At the end of the reaction the reaction mixture was flushed through a short pad of silica using EtOAc to elute. The amine product was isolated by flash chromatography on silica gel and its ee was determined by chiral GC.

700 MHz NMR reactions for hydride detection:

To a 5 mm NMR tube were added the catalyst (3 mol%), and formic acid/triethylamine 5:2 complex (0.6 mL) followed by 0.05 mL of C_6D_6. The reaction was followed by ^{1}H-NMR with hydride detection.

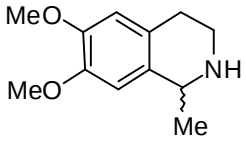
1-Phenylethanol 113



This is a known compound.

Enantiomeric excess and conversion determined by GC analysis (Chrompak cyclodextrin-β-236M-19 50m, T = 115 ^{o}C, P = 15 psi, gas H_2, Ketone 9.81 min, *R* isomer 15.32 min, *S* isomer 16.41 min). δ_H (300 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 4.87 (1H, q, *J* 6.5, -C*H*), 2.07 (1H, br s, -O*H*), 1.48 (3H, d, *J* 6.5, -CH_3); δ_C (75 MHz, $CDCl_3$): 145.20, 127.90(2C), 126.87, 124.78(2C), 69.81, 24.55.[173,205]

6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 166 (Salsolidine)



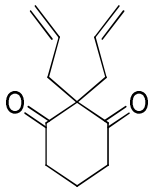
This is a known compound.

Enantiomeric excess and conversion determined by GC analysis (Chrompak cyclodextrin-β-236M-19 50m, T = 170 ^{o}C, P = 15 psi, gas H_2, Imine 38.46 min, *S* isomer 35.12 min, *R* isomer 35.94 min). δ_H (300 MHz, $CDCl_3$) 6.61 (1H, s, -C*H* of Ar), 6.57 (1H, s, -C*H* of Ar), 4.14 (1H, q, *J* 6.6, -C*H*), 3.85 (6H, s, 2 x -OCH_3), 3.36-3.24 (1H, m, -CH_2), 3.12-3.00 (1H, m, -CH_2), 2.94-2.79 (1H, m, -CH_2), 2.78-2.66 (1H, m, -CH_2), 1.50 (3H, d, *J* 6.6, -CH_3); δ_C (75 MHz, $CDCl_3$) 147.36, 147.10, 128.61, 124.48, 110.91, 108.23, 55.43, 55.29, 50.48, 39.95, 27.01, 21.07.[202,262]

3.6 Synthesis of hindered ketones

3.6.1 Derivatives of 1,3-cyclohexadione

2,2-Di(prop-2-en-1-yl)cyclohexane-1,3-dione (315).

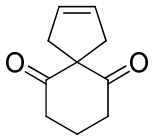


This is a known compound and the method is based on a reported synthesis.[241]

KF was added to a mixture of Celite stirred in H_2O then stirred for 40 min. The Celite was filtered off then dried in a desiccator overnight. The KF-Celite (1.77 g) was added to a mixture of cyclohexane-1,3-dione **314** (0.500 g, 4.46 mmol) and allyl bromide (1.16 mL, 13.38 mmol) in CH_3CN (15 mL). The mixture was heated at

75°C for 6 h. The reaction mixture was filtered under reduced pressure, washed with CH_3CN (2 x 15 mL) and the solvent evaporated to give a crude product as a yellow oil. The crude compound was purified by column chromatography using hexane:EtOAc (80:20) to give 2,2-di(prop-2-en-1-yl)cyclohexane-1,3-dione **315** as a colourless oil (0.286 g, 1.48 mmol, 33%). ν_{max}(film): 3029, 1692, 1723, 1692, 1210, 998, 919 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 5.60-5.46 (2H, m, 2 x -C*H*=CH_2), 5.04-4.98 (4H, m, 2 x -CH=C*H*$_2$), 2.55-2.48 (8H, br s, 2 x -C*H*$_2$CO, 2 x -C*H*$_2$-CH=CH_2), 1.94-1.85 (2H, m, -C*H*$_2$-); δ_C (75 MHz, $CDCl_3$): 210.33(2C), 132.40(2C), 119.31(2C), 68.25, 40.88(2C), 39.55(2C), 16.4; *m/z* (ESI+) 215.0 (M+Na). HRMS Found 215.1039 ($C_{12}H_{16}O_2Na$ requires 215.1043). The spectroscopic data were in agreement with literature values. [241]

Spiro[4,5]dec-2-ene-6,10-dione (312).

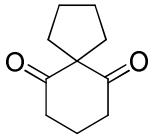


This is a known compound and the method is based on a reported synthesis.[241a]

To a solution of 2,2-di(prop-2-en-1-yl)cyclohexane-1,3-dione **315** (0.300 g, 1.562 mmol) in dry DCM (18 mL) was added Grubb's Catalyst 1st generation (66 mg, 5.15 mol%) under an inert atmosphere. The solution was stirred at 22-23 ^oC for 27 h. The colour of the reaction changed from purple to brown. The reaction mixture was concentrated on a rotary evaporator to give a crude residue. The crude compound was purified by column chromatography using hexane:EtOAc (92:8) to give spiro[4,5]dec-2-ene-6,10-dione **312** as white solid (0.207 g, 1.262 mmol, 80%). Mp 58-60 ^oC; ν_{max} 3053, 2913, 1723, 1687, 1434, 1340, 1320, 1262, 1114, 1011, 912

cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.54 (2H, m, -C*H*=C*H*), 2.87 (4H, m, -CH_2-CH=CH-CH_2-), 2.72 (4H, br t, *J* 7.5, -CH_2-CO-), 2.04-1.95 (2H, m, -CH_2-); δc (75 MHz, $CDCl_3$) 207.03(2C), 127.02(2C), 39.08(2C), 37.54(2C), 17.48; m/z ESI-MS $[M+Na]^+$ 187.2; HRMS found 187.0721 ($C_{10}H_{12}O_2Na$ requires 187.0730, error = 4.4 ppm). The spectroscopic data were in agreement with literature values. [241a]

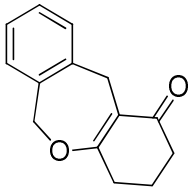
Spiro[4,5]decane-6,10-dione (316).



This is a known compound.[263]

A solution of spiro[4,5]dec-2-ene-6,10-dione **312** (0.100 g, 0.610 mmol) in dry methanol (10 mL) containing Pd/C (10 % on carbon) (65 mg) under atmospheric pressure of hydrogen at 21-22 ^oC was stirred for 18 h. The reaction mixture was filtered through Celite and filtrate was concentrated on a rotary evaporator to give a crude residue. The crude compound was purified by column chromatography using hexane:EtOAc (90:10) to give spiro[4,5]decane-6,10-dione **316** as a colourless oil (0.100 g, 0.602 mmol, 99%). ν_{max} 2954, 2870, 1722, 1689, 1448, 1314, 1273, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.67 (4H, t, *J* 6.0, -CH_2CO-), 2.08-2.03 (4H, m,-C(C*H*)$_2$-), 2.00-1.93 (2H, m, -CH_2-CH_2CO-), 1.69-1.65 (4H, m,-CH_2-CH_2-); δc (75 MHz, $CDCl_3$) 208.62(2C), 72.49, 37.91(2C), 33.17(2C), 26.42(2C), 17.70. The spectroscopic data were in agreement with literature values. [263]

3,4,6,11-Tetrahydrodibenzo[*b,e*]oxepin-1(2*H*)-one (318).

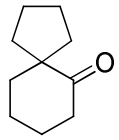


This is a novel compound.

To a mixture of K_2CO_3 (3.08 g, 11.16 mmol, 5 eq) in dry acetone (10 mL) was added cyclohexane-1,3-dione **314** (0.250 g, 2.232 mmol) under an inert atmosphere. The mixture was stirred at 26-27 ^oC for 10-15 min. To this mixture, 1,2-(dibromomethyl)benzene (0.550g, 2.232 mmol, 1.0 eq) was added and the resulting mixture was stirred at 55-56 ^oC for 50 h. The reaction mixture was cooled to room temperature, filtered through Celite and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (93:7) to give 3,4,6,11-tetrahydrodibenzo[*b*,*e*]oxepin-1(2*H*)-one **318** as a colourless oil (0.110 g, 0.514 mmol, 23%). ν_{max} 2946, 1708, 1640, 1597, 1458, 1426, 1385, 1362, 1293, 1249, 1183, 1106, 1005, 987, 871, 750, 674 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33-7.21 (4H, m, -CH of -C_6H_4-), 5.25 (2H, s, -CH_2-C_6H_4-CH_2-O), 3.92 (2H, s, -CH_2-C_6H_4-CH_2-O), 2.39-2.31 (4H, m, -CH_2-CH_2-CH_2CO), 1.89-1.80 (2H, m, -CH_2CO); δc (300 MHz, $CDCl_3$) 197.80, 172.46, 141.08, 134.34, 128.81, 128.03, 127.64, 126.29, 112.07, 70.58, 36.30, 30.38, 26.96, 19.74; m/z ESI-MS $[M+Na]^+$ 237.1; HRMS found 215.1070 ($C_{14}H_{14}O_2H^+$ requires 215.1067, error = -1.9 ppm).

3.6.2 Derivatives of cyclohexanone

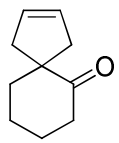
Spiro[4,5]decane-6-one (320).



This is a known compound and the method is based on a reported synthesis.[242]

To a mixture of KO^{t}Bu (2.54 g, 22.62 mmol, 2.22 eq) in dry toluene (20 mL) was added cyclohexanone **319** (1.0 g, 10.189 mmol) under an inert atmosphere. The mixture was stirred at 20-21 ^oC for 1 h. To this mixture, 1,4-dibromobutane (1.216 mL, 10.189 mmol, 1.0 eq) was added dropwise. The resulting mixture was stirred at 110-111 ^oC for 5 h. The reaction mixture was cooled to room temperature, diluted with water (10 mL) and HCl (15%, 20 mL). The mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give crude oil. The oil was purified by column chromatography using n-pentane: diethyl ether (98:2) to give spiro[4,5]decane-6-one **320** as a colourless oil (0.330 g, 2.171 mmol, 21%). ν_{max} 2934, 2863, 1703, 1443, 1345, 1311, 1126, 954 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.42-2.38 (2H, m, -C*H*$_2$CO-), 2.10-2.02 (2H, m, -CH$_2$-C-C*H*$_2$-), 1.86-1.78 (2H, m, -C*H*$_2$-CH$_2$CO-), 1.72-1.70 (4H, m, -C*H*$_2$-C*H*$_2$-CH$_2$-CH$_2$CO-), 1.63-1.54 (4H, m, -C*H*$_2$-C*H*$_2$-), 1.44-1.35 (2H, m, -C*H*$_2$-C-CH$_2$-); δc (300 MHz, $CDCl_3$) 214.71, 56.82, 39.92, 39.43, 35.42(2C), 27.32, 25.22(2C), 22.82; m/z ESI-MS $[M+Na]^+$ 175.0; HRMS found 175.1099 ($C_{10}H_{16}ONa$ requires 175.1093, error = -3.4 ppm). The spectroscopic data were in agreement with literature values. [242]

Spiro[4,5]dec-2-en-6-one (321).

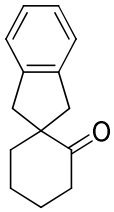


This is a known compound and the method is based on a reported synthesis.[243]

A solution of Na (0.938 g, 40.816 mmol, 2.0 eq) in *tert*-amyl alcohol (20 mL) was evaporated under reduced pressure to give white solid and added dry toluene (30

mL). To this mixture was added cyclohexanone **319** (2.0 g, 20.408 mmol) followed by 1,4-dichloro-2-butene (2.530 g, 20.408 mmol, 1.0 eq) under an inert atmosphere. The mixture was stirred at 110-111 ^{o}C for 48 h. The reaction mixture was cooled to room temperature, diluted with water (5 mL) and HCl (15%, 10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and evaporated to give crude oil. The oil was purified by column chromatography using n-pentane: diethyl ether (95:5) to give spiro[4,5]dec-2-en-6-one **321** as a colourless oil (0.500 g, 3.33 mmol, 16%). ν_{max} 3056, 2928, 2850, 1702, 1623, 1449, 1351, 1336, 1271 1130, 1056, 940, 897, 666 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.55 (2H, s, -C*H*=C*H*-), 2.87 (2H, d, *J* 12.0, -C*H*H-CH=CH-C*H*H-), 2.44 (2H, t, *J* 7.5, -CH_2CO), 2.20 (2H, d, *J* 12.0, -C*H*H-CH=CH-C*H*H-), 1.89-1.71 (6H, m, -(CH_2)$_3$-CH_2CO); δc (300 MHz, $CDCl_3$) 127.82(2C), 41.72(2C), 40.11, 39.48, 27.19, 22.25; m/z ESI-MS $[M+Na]^+$ 173.1; HRMS found 151.1116 ($C_{10}H_{14}ONa$ requires 151.1117, error = 0.6 ppm). The spectroscopic data were in agreement with literature values.[243]

1',3'- Dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-one (322).



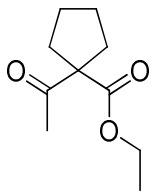
This is a known compound.[244]

To a mixture of KO^{t}Bu (1.27 g, 11.308 mmol, 2.22 eq) in dry ^{t}BuOH (12.5 mL) was added cyclohexanone **319** (0.500 g, 5.094 mmol) under an inert atmosphere. The mixture was stirred at 26-27 ^{o}C for 10-15 min. To this mixture, 1,2-(dibromomethyl)benzene (1.34 g, 5.094 mmol, 1.0 eq) was added and the resulting

mixture was stirred at 26-27 ^{o}C for 24 h. The reaction mixture was concentrated on a rotary evaporator to give a residue. The residue was diluted with water (10 mL) and 15% HCl (10 mL). The mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (95:5) to give 1',3'- dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-one **322** as a colourless oil (0.460 g, 2.300 mmol, 45%). ν_{max} 3023, 2930, 2860, 1700, 1485, 1444, 1428, 1337, 1311, 1220, 1127, 744, 727 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.18-7.12 (4H, m, -CH of -C_6H_4-), 3.46 (2H, d, *J* 12.0, -C*H*H-C_6H_4-C*H*H-), 2.82 (2H, d, *J* 12.0, -CH*H*-C_6H_4-CH*H*-), 2.49 (2H, t, *J* 6.0, -CH_2CO), 1.92-1.89 (2H, m, -CH_2-CH_2CO), 1.87-1.84 (2H, m, -CH_2-CH_2-CH_2CO), 1.83-1.76 (2H, m, -CH_2-CH_2-CH_2-CH_2CO); δc (300 MHz, $CDCl_3$) 212.93, 140.84(2C), 126.50(2C), 124.84(2C), 57.22, 41.31(2C), 39.53, 39.13, 27.48, 22.21; m/z ESI-MS $[M+Na]^+$ 223.2; HRMS found 223.1091 ($C_{14}H_{16}ONa$ requires 223.1093, error = 0.9 ppm). The spectroscopic data were in agreement with literature values. [244]

3.6.3 Derivatives of ethyl acetoacetate

Ethyl 1-acetylcyclopentanecarboxylate (334).

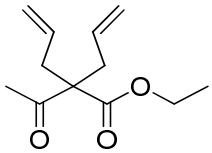


This is a known compound and the method is based on a reported synthesis.[246]

To a mixture of KO^{t}Bu (2.65 g, 19.210 mmol, 2.5 eq) in DMSO (15 mL) was added ethyl acetoacetate **333** (1.0 g, 7.684 mmol) under an inert atmosphere. The mixture

was stirred at 21-22 ^{o}C for 10 min. 1,4-Dibromobutane (0.918 mL, 7.684 mmol, 1.0 eq) was then added dropwise. The resulting mixture was stirred at 21-22 ^{o}C for 3 days. The reaction mixture was poured into ice-cold water and extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (95:5) to give ethyl 1-acetylcyclopentanecarboxylate **334** as a colourless oil (1.0 g, 5.434 mmol, 70%). ν_{max} 2959, 2874, 1739, 1711, 1623, 1446, 1356, 1240, 1147, 1097, 1052, 1026, 857 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.23-4.16 (2H, q, *J* 7.0, -OC*H*$_2$CH$_3$), 2.16 (3H, s, -COC*H*$_3$), 2.13-2.08 (4H, m, -C*H*$_2$-C-C*H*$_2$-), 1.71-1.60 (4H, m, -C*H*$_2$-C*H*$_2$-), 1.26 (3H, t, *J* 7.0, -OCH$_2$C*H*$_3$); δc (300 MHz, $CDCl_3$) 61.31, 32.96(2C), 26.04, 25.64(2C), 14.02; m/z ESI-MS $[M+Na]^+$ 207.2; HRMS found 207.0992 ($C_{10}H_{16}O_3Na$ requires 207.0992, error = -0.4 ppm). The spectroscopic data were in agreement with literature values. [246]

Ethyl 2-acetyl-2-(prop-2-en-1-yl)pent-4-enoate (**335).**

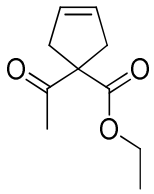


This is a known compound and the method is based on a reported synthesis.[247]

To a mixture of K_2CO_3 (3.22 g, 23.359 mmol, 3.04 eq) in DMF (10 mL) was added ethyl acetoacetate **333** (1.0 g, 7.684 mmol) under an inert atmosphere. The resulting mixture was stirred at 21-22 ^{o}C for 10 min. To this, a solution of allyl bromide (1.649 mL, 19.056 mmol, 2.48 eq) in DMF (5 mL) was added dropwise. The resulting mixture was heated to 80 ^{o}C for 20 h. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with diethyl ether (3 x

20 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (92:8) to give ethyl 2-acetyl-2-(prop-2-en-1-yl)pent-4-enoate **335** as a colourless oil (1.5 g, 7.142 mmol, 93%). ν_{max} 3079 2981, 1740, 1715, 1641, 1442, 1356, 1278, 1207, 1179, 1138, 1017, 994, 918, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.67-5.53 (2H, m, 2 x -CH_2-C*H*=CH_2), 5.14-5.08 (4H, m, 2 x -CH_2-CH=C*H*$_2$), 4.24-4.17 (2H, q, *J* 7.0, -OC*H*$_2$$CH_3$), 2.69-2.54 (4H, m, 2 x -C*H*$_2$-CH=CH_2), 2.14 (3H, s, -COC*H*$_3$), 1.27 (3H, t, *J* 7.0, -OCH_2C*H*$_3$); δc (300 MHz, $CDCl_3$) 132.16(2C), 119.15(2C), 63.20, 61.38, 35.92(2C), 26.91, 14.10; m/z ESI-MS $[M+Na]^+$ 233.2; HRMS found 233.1153 ($C_{12}H_{18}O_3Na$ requires 233.1148, error = -2.0 ppm). The spectroscopic data were in agreement with literature values. [247]

Ethyl 1-acetylcyclopent-3-ene-1-carboxylate (336).

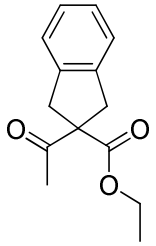


The method is based on a reported synthesis.[247] This is a known compound.[264]

To a solution of ethyl 2-acetyl-2-(prop-2-en-1-yl)pent-4-enoate **335** (0.250 g, 1.190 mmol) in dry DCM (60 mL) was added Grubb's 1st generation catalyst (49 mg, 5 mol%) under an inert atmosphere and the resulting mixture was stirred for 24 h at 22-23 ^oC. The colour of the reaction changed from purple to brown. The reaction mixture was concentrated on a rotary evaporator to give a crude residue. The crude compound was purified by column chromatography using n-pentane: diethyl ether (94:6) to give ethyl 1-acetylcyclopent-3-ene-1-carboxylate **336** as a colourless oil (0.200 g, 1.099 mmol, 92%). ν_{max} 3063, 2983, 1713, 1445, 1357, 1260, 1230, 1153,

1096, 1071, 1017 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.59 (2H, br m, -C*H*=C*H*-), 4.25-4.18 (2H, q, *J* 7.0, -OC$H_2$$CH_3$), 2.94 (4H, br s, -C$H_2$-CH=CH-C$H_2$-), 2.19 (3H, s, -COC$H_3$), 1.27 (3H, t, *J* 7.0, -$OCH_2C$$H_3$); δc (300 MHz, $CDCl_3$) 127.71(2C), 61.60, 39.22(2C), 25.91, 14.00; m/z ESI-MS $[M+Na]^+$ 205.1; HRMS found 205.0837 ($C_{10}H_{14}O_3Na$ requires 205.0835, error = -1.2 ppm). The spectroscopic data were in agreement with literature values. [264]

Ethyl 2-acetyl-2,3-dihydro-1H-indene-2-carboxylate (337).



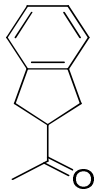
This is a known compound and the method is the same as for a reported synthesis.[248]

To a mixture of TBAB (31 mg, 0.0958 mmol, 0.05 eq) in 48% NaOH solution (1.1 mL) was added a solution of 1,2-(dibromomethyl)benzene (0.500g, 1.894 mmol) in toluene (2.5 mL). To this, a solution of ethyl acetoacetate **333** (0.240 mL, 1.894 mmol, 1.0 eq) in toluene (0.5 mL) was added dropwise and during addition the temperature increased from 22 ^oC to 38-40 ^oC. The reaction mixture was stirred at 22 ^oC for 3.5 h. The residue was diluted with water (20 mL) and extracted with toluene (2 x 25 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (95:5) to give ethyl 2-acetyl-2,3-dihydro-1H-indene-2-carboxylate **337** as a colourless oil (0.310 g, 1.336 mmol, 70%). ν_{max} 2981, 1710, 1486, 1460, 1336, 1269, 1233, 1150, 1072, 1017, 858, 743 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.17-7.14 (4H, m, -CH of -C_6H_4-), 4.25-4.18 (2H, q, *J* 7.0, -OC$H_2$$CH_3$),

3.53-3.46 (4H, m, -C*H*$_2$-C$_6$H$_4$-C*H*$_2$-), 2.23 (3H, s, -COC*H*$_3$), 1.26 (3H, t, *J* 7.0, -OCH$_2$C*H*$_3$); δc (300 MHz, $CDCl_3$) 140.21(2C), 127.35(2C), 124.67(2C), 62.21, 38.38(2C), 26.50, 14.42; m/z ESI-MS $[M+Na]^+$ 255.1; HRMS found 225.0997 ($C_{14}H_{16}O_3Na$ requires 225.0992, error = -2.0 ppm). The spectroscopic data were in agreement with literature values. [248]

3.6.4 Synthesis of 1-(2-ethyl-2,3-Dihydro-1H-inden-2-yl)ethanone (340).

1-(2,3-Dihydro-1H-inden-2-yl)ethanone (339).

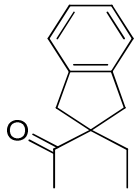


This is a known compound and the method is the same as for a reported synthesis.[249]

To a mixture of TBAB (0.161 g, 0.50 mmol, 0.05 eq) in 48% NaOH solution (5 mL) was added solution of 1,2-(dibromomethyl)benzene (2.640 g, 10.0 mmol) in toluene (6 mL). To this, a solution of acetylacetone **338** (1.0 g, 10.0 mmol, 1.0 eq) in toluene (6 mL) was added dropwise and during addition the temperature increased from 22 ^oC to 38-40 ^oC. The reaction mixture was heated to 80-85 ^oC for 5 h. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with toluene (2 x 35 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane: ethyl acetate (93:7) to give 1-(2,3-dihydro-1H-inden-2-yl)ethanone **339** as a colourless oil (0.600 g, 3.75 mmol, 41%). ν_{max} 3022, 2939, 2849, 1708, 1484, 1459, 1359, 1199, 1163, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.22-7.14 (4H, m, -CH of -C$_6$*H*$_4$-), 3.50-3.38 (1H, m, -C*H*COCH$_3$), 3.19 (2H, d, *J* 7.5, -

C*H*H-C_6H_4-C*H*H-), 3.21 (2H, d, *J* 7.5, -CH*H*-C_6H_4-CH*H*-), 2.24 (3H, s, -COCH_3); δc (300 MHz, $CDCl_3$) 209.30, 141.43(2C), 126.61(2C), 124.39(2C), 51.86, 34.94(2C), 28.47; m/z ESI-MS $[M+Na]^+$ 183.1; HRMS found 183.0785 ($C_{11}H_{12}ONa$ requires 183.0780, error = -2.8 ppm). The spectroscopic data were in agreement with literature values. [249]

1-(2-Ethyl-2,3-dihydro-1H-inden-2-yl)ethanone (340).



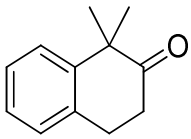
This is a known compound and the method is based on a reported synthesis.[249]

To a mixture of KO^{t}Bu (0.522 g, 4.657 mmol, 1.50 eq) in THF (15 mL) was added 1-(2,3-dihydro-1H-inden-2-yl)ethanone **339** (0.500 g, 3.125 mmol) under an inert atmosphere. The resulting mixture was stirred at 21-22 ^oC for 10 min and cooled to -20 ^oC. To this, ethyl iodide (0.275 mL, 3.438 mmol, 1.10 eq) was added dropwise. The resulting mixture was stirred at -20 ^oC for 3 h and warmed to room temperature. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane: ethyl acetate (92:8) to give 1-(2-ethyl-2,3-dihydro-1H-inden-2-yl)ethanone **340** as a colourless oil (0.325 g, 1.728 mmol, 55%). ν_{max} 3023, 2964, 2931, 1701, 1484, 1459, 1355, 1218, 1135, 783, 743, 722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19-7.12 (4H, m, -CH of -C_6H_4-), 3.37 (2H, d, *J* 16.5, -C*H*H-C_6H_4-C*H*H-), 2.85 (2H, d, *J* 16.5, -CH*H*-C_6H_4-CH*H*-), 2.19 (3H, s, -COCH_3), 1.80 (2H, q, *J* 7.5, -CH_2CH$_3$), 0.83 (3H, t, *J* 7.5,

-CH_2CH_3); δc (300 MHz, $CDCl_3$) 141.20(2C), 126.51(2C), 124.53 (2C), 60.81, 40.28(2C), 30.82, 25.80, 9.56; m/z ESI-MS $[M+Na]^+$ 211.1; HRMS found 211.1153 ($C_{13}H_{16}ONa$ requires 211.1094, error = -0.1 ppm). The spectroscopic data were in agreement with literature values. [249]

3.6.5 Derivatives of β-tetralone

1,1-Dimethyl-3,4-dihydronaphthalen-2(1H)-one (349).

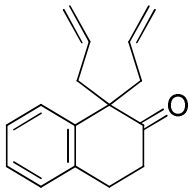


This is a known compound and the method is based on a reported synthesis.[250]

To a mixture of β-tetralone **348** (0.750 g, 5.136 mmol), TBAS (0.278 g, 0.822 mmol, 0.16 eq) and methyl iodide (0.959 mL, 15.408 mmol, 3.0 eq) in THF (3 mL) was rapidly added 50% KOH solution in H_2O (5 mL). The reaction mixture became warm and turned blue. The reaction mixture was stirred for 30 min during which time the colour changed from blue to green and finally light brown. The reaction mixture was poured into water (20 mL) and extracted with diethyl ether (2 x 25 mL). The combined organic layer was washed with sat. NH_4Cl soln (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:EtOAc (96:4) to give 1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one **349** as a white solid (0.775 g, 4.454 mmol, 86%). ν_{max} 2972, 2933, 1709, 1488, 1449, 1380, 1244, 1091, 1042, 758, 742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37-7.34 (1H, m, -CH of -C_6H_4-), 7.30-7.23 (1H, m, -CH of -C_6H_4-), 7.20-7.18 (2H, m, -CH of -C_6H_4-), 3.10 (2H, t, *J* 6.7, -CH_2-C_6H_4-), 2.69 (2H, d, *J* 6.7, -CH_2CO-), 1.44 (6H, br s, -$C(CH_3)_2$-); δc (300 MHz, $CDCl_3$)

214.76, 143.52, 135.15, 128.13, 127.10, 126.37, 126.13, 47.76, 37.20, 28.59, 26.89(2C); m/z ESI-MS $[M+Na]^+$ 175.2; HRMS found 175.1118 ($C_{12}H_{14}O$+H requires 175.1117, error = -0.6 ppm). The spectroscopic data were in agreement with literature values. [250]

1,1-Di(prop-2-en-1-yl)-3,4-dihydronaphthalen-2(1H)-one (350).

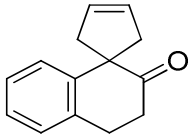


This is a known compound[265] and method is used same as for ethyl 2-acetyl-2-allylpent-4-enoate.[247]

To a mixture of K_2CO_3 (1.44 g, 10.397 mmol, 3.04 eq) in DMF (15 mL) was added β-tetralone **348** (0.500 g, 3.420 mmol) under an inert atmosphere and the resulting mixture was stirred at 21-22 ^oC for 10 min. To this, a solution of allyl bromide (0.734 mL, 8.482 mmol, 2.48 eq) in DMF (5 mL) was added dropwise. The resulting mixture was heated to 80 ^oC for 4 h. The reaction mixture was cooled to room temperature, diluted with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using n-pentane: diethyl ether (97:3) to give 1,1-di(prop-2-en-1-yl)-3,4-dihydronaphthalen-2(1H)-one **350** as a colourless oil (0.500 g, 2.212 mmol, 64%). ν_{max} 3076, 2909, 1710, 1639, 1489, 1444, 1416, 1226, 1167, 997, 916, 760, 737 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35-7.28 (2H, m, 2 -CH of -C_6H_4-), 7.22-7.14 (2H, m, 2 -CH of -C_6H_4-), 5.44-5.30 (2H, m, 2 x -CH_2-C*H*=CH_2), 4.95-4.85 (4H, m, 2 x -CH_2-CH=CH_2), 2.96 (2H, t, *J* 6.0, -CH_2-C_6H_4-), 2.78 (2H, d, *J* 12.0, 8.0, 2 x -C*H*H-CH=CH_2), 2.54 (2H, t,

J 6.0, -C*H*$_2$CO-), 2.52-2.47 (2H, m, 2 x -CH*H*-CH=CH$_2$), δc (300 MHz, CDCl$_3$) 139.12, 136.97, 133.34(2C), 128.00, 126.98, 126.87, 126.34, 118.28(2C), 55.98, 45.06(2C), 40.28, 27.83; m/z ESI-MS $[M+H]^+$ 227.2; HRMS found 249.1248 ($C_{16}H_{18}ONa$ requires 249.1250, error = 0.7 ppm). The spectroscopic data were in agreement with literature values. [265]

3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-one (351).

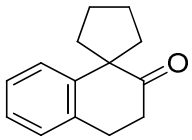


This is a novel compound and the method is used is the same as for spiro[4,5]dec-2-ene-6,10-dione.

To a solution of 1,1-diallyl-3,4-dihydronaphthalen-2(1H)-one **350** (0.400 g, 1.770 mmol) in dry DCM (80 mL) was added Grubb's 1st generation catalyst (72.8 mg, 5 mol%) under an inert atmosphere and the resulting mixture was stirred for 24 h at 22-23 ^{o}C. The colour of the reaction changed from purple to brown. The reaction mixture was concentrated on a rotary evaporator to give a crude residue. The crude compound was purified by column chromatography using n-pentane: diethyl ether (95:5) to give 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-one **351** as a colourless oil (0.295 g, 1.489 mmol, 84%). ν_{max} 3055, 2916, 2846, 1709, 1488, 1451, 1346, 1234, 1140, 1048, 972, 788, 754, 666 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.27-7.21 (2H, m, 2 -CH of -C$_6$*H*$_4$-), 7.19-7.13 (2H, m, 2 -CH of -C$_6$*H*$_4$-), 5.71 (2H, m, -C*H*=C*H*-), 3.22-3.15 (2H, m, -C*H*H-CH=CH-C*H*H-), 3.10 (2H, t, *J* 7.5, -C*H*$_2$-C$_6$H$_4$-), 2.73 (2H, t, *J* 7.5, -C*H*$_2$CO-), 2.68-2.59 (2H, m, -CH*H*-CH=CH-CH*H*-); δc (300 MHz, CDCl$_3$) 212.91, 144.78, 134.59, 128.04(2C), 127.67, 127.37, 126.32, 126.14,

46.83(2C), 37.63, 28.90; m/z ESI-MS $[M+Na]^+$ 221.2; HRMS found 221.0935 ($C_{14}H_{14}ONa$ requires 221.0937, error = 0.8 ppm).

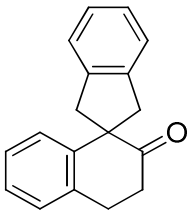
3',4'-Dihydro-2'H-spiro[cyclopentane-1,1'-naphthalene]-2'-one (352).



This is a known compound[266] and the method used is the same as for spiro[4,5]decane-6,10-dione.

A solution of 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-one **351** (0.198 g, 1.000 mmol) in dry EtOAc (20 mL) containing added Pd/C (10 % on carbon) (100 mg) was stirred under an atmospheric pressure of hydrogen at 21-22 ^oC for 24 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator to give a crude residue. The crude compound was purified by column chromatography using n-pentane: diethyl ether (95.5:4.5) to give 3',4'-dihydro-2'H-spiro[cyclopentane-1,1'-naphthalene]-2'-one **352** as a colourless oil (0.140 g, 0.700 mmol, 70%). ν_{max} 2950, 2867, 1706, 1487, 1449, 1346, 1236, 1045, 936, 754, 742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29-7.20 (2H, m, -CH of -C_6H_4-), 7.18-7.14 (2H, m, -CH of -C_6H_4-), 3.09 (2H, t, *J* 6.5, -CH_2-CH_2CO), 2.69 (2H, t, *J* 6.5, -CH_2-CH_2CO-), 2.39-2.29 (2H, m, -CH*H*CH_2CH_2CH*H*-), 1.93-1.81 (6H, m, -C*H*HCH_2CH_2C*H*H-); δc (300 MHz, $CDCl_3$) 213.75, 143.83, 135.90, 127.85, 126.96, 126.14(2C), 59.25, 38.35(2C), 37.18, 28.77, 26.63(2C); m/z ESI-MS $[M+Na]^+$ 223.1; HRMS found 223.1094 ($C_{14}H_{16}ONa$ requires 223.1093, error = -0.2 ppm). The spectroscopic data were in agreement with literature values. [252]

1,3,3',4'-Tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-one (353).

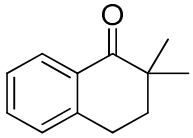


This is a novel compound.

To a mixture of TBAB (27.7 mg, 0.0855 mmol, 0.05 eq) in 48% NaOH solution (1.1 mL) was added solution of 1,2-(dibromomethyl)benzene (0.451 g, 1.710 mmol) in toluene (2.5 mL). To this, a solution of β-tetralone **348** (0.250 g, 1.710 mmol) in toluene (0.5 mL) was added dropwise during which the temperature increased from 22 ^{o}C to 38-40 ^{o}C. The reaction mixture was stirred at 22-23 ^{o}C for 4 h. The residue was diluted with water (20 mL) and extracted with toluene (2 x 25 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using n-pentane:diethyl ether (88:12) to give 1,3,3',4'-tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-one **353** as a white solid (0.300 g, 1.210 mmol, 70%). Mp 128-130 ^{o}C; ν_{max} 3019, 2953, 2893, 1699, 1485, 1452, 1233, 1146, 1017, 760, 750, 743 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.21-7.14 (6H, m, 4 -CH of -C_6H_4-, 2 -CH of -C_6H_4-), 7.13-7.08 (2H, m, 2-CH of -C_6H_4-), 3.79 (2H, d, *J* 16.5, -C*H*H-C_6H_4-C*H*H-), 3.21 (2H, d, *J* 16.5, -CH*H*-C_6H_4-CH*H*-), 3.18 (2H, t, *J* 6.0, -CH_2-CH_2CO-), 2.77 (2H, t, *J* 6.0, -CH_2CO-); δc (300 MHz, $CDCl_3$) 212.47, 142.97, 140.73(2C), 135.31, 128.00, 127.72, 126.93(2C), 126.65, 125.95, 124.17(2C), 58.93, 44.84(2C), 37.30, 28.62; m/z ESI-MS $[M+Na]^+$ 271.1; HRMS found 249.1275 ($C_{18}H_{16}O$ +H requires 249.1274, error = -0.3 ppm).

3.6.6 Derivatives of α-tetralone

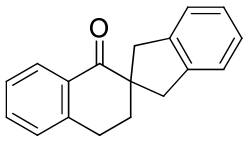
2,2-Dimethyl-3,4-dihydronaphthalen-1(2H)-one (355).



This is a known compound and the method is based on a reported synthesis.[251]

To a suspension of NaH (0.957 g, 23.94 mmol, 3.54 eq) into THF (25 mL) was added a solution of α-tetralone **354** (1.0 g, 6.840 mmol) in THF (2.5 mL). The reaction mixture was stirred for 15 min. To this, iodomethane (1.49 mL, 23.94 mmol, 3.54 eq) was added dropwise. The resulting mixture was stirred at 40 ^{o}C for 45 min. The reaction mixture was cooled to room temperature and then in ice cold water. The reaction mixture was quenched by slow addition of water. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water, brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated to give a crude oil. The oil was purified by column chromatography using hexane:ethyl acetate (90:10) to give 2,2-dimethyl-3,4-dihydronaphthalen-1(2H)-one **355** as an oil (0.780 g, 4.483 mmol, 65 %). δ_H (300 MHz, $CDCl_3$) 8.04 (1H, dd, *J* 1.3, 7.0, -CH of -C_6H_4-), 7.45 (1H, dt, *J* 1.5, 7.3 -CH of -C_6H_4-), 7.30 (1H, t, *J* 7.5, -CH of -C_6H_4-), 7.22 (1H, d, *J* 8.1, -CH of -C_6H_4-), 2.98 (2H, t, *J* 6.4, -CH_2-C_6H_4-), 1.98 (2H, d, *J* 6.4, -CH_2CO-), 1.22 (6H, br s, -C(CH_3)$_2$-); δc (300 MHz, $CDCl_3$) 143.35, 132.95, 131.37, 128.63, 127.93, 126.54, 41.56, 36.55, 25.65, 24.31(2C). The spectroscopic data were in agreement with literature values. [251]

1,3,3',4'-Tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-one (356).



This is a known compound[267] and the method used is the same as for 1',3'- dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-one.[244]

To a mixture of KO^{t}Bu (0.426 g, 3.80 mmol, 2.22 eq) in dry ^{t}BuOH (10 mL) was added α-tetralone **354** (0.250 g, 1.710 mmol) under an inert atmosphere and the resulting solution was stirred at 26-27 ^{o}C for 10-15 min. To this mixture, 1,2-(dibromomethyl)benzene (0.451 g, 1.710 mmol, 1.0 eq) was added and resulting mixture was stirred at 26-27 ^{o}C for 18 h. The reaction mixture was concentrated on a rotary evaporator to give a residue. The residue was diluted with water (10 mL) and 15% HCl (10 mL). The mixture was extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude residue. The oil was purified by column chromatography using hexane:EtOAc (94:6) to give 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-one **356** as a white solid (0.250 g, 1.008 mmol, 58%). Mp 88-90 ^{o}C; ν_{max} 3346, 3071, 2921, 2842, 1764, 1668, 1599, 1486, 1455, 1427, 1231, 1226, 1155, 906, 749, 739, 715 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, dd, *J* 6.0, 1.2, -CH of -C_6H_4-), 7.48 (1H, dt, *J* 6.0, 1.2, -CH of -C_6H_4-), 7.32 (1H, t, *J* 3.0, -CH of -C_6H_4-), 7.25 (1H, t, *J* 3.0, -CH of -C_6H_4-), 7.20-7.15 (4H, m, -CH of -C_6H_4-), 3.49 (2H, d, *J* 12.0, -C*H*H-C_6H_4-C*H*H-), 3.08 (2H, t, *J* 4.5, -CH_2-CH_2-C_6H_4-), 2.97 (2H, d, *J* 12.0, -CH*H*-C_6H_4-CH*H*-), 2.22 (2H, t, *J* 4.5, -CH_2-CO); δc (300 MHz, $CDCl_3$) 143.30, 141.10(2C), 133.22, 131.59, 128.68, 128.18, 126.71, 126.59(2C), 124.57(2C), 53.50, 41.31(2C), 33.86, 26.08; m/z ESI-MS $[M+Na]^+$ 271.1; HRMS found 271.1093

($C_{18}H_{16}ONa$ requires 271.1093, error = -0.1 ppm). The spectroscopic data were in agreement with literature values. [267]

3.7 Asymmetric transfer hydrogenation of α,α-disubstituted ketones

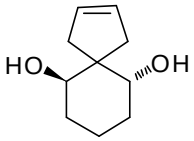
General procedure for asymmetric transfer hydrogenation of 1,3-diketone derivatives:

A mixture of catalyst (2 mol%) in FA:TEA (5:2) (0.3 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, ketone (0.3 mmol) was added and the resulting mixture was stirred at 28 ^{o}C for 21-91 h under an inert atmosphere. The completion of the reaction was confirmed by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol. The crude compound was purified by flash column chromatography.

General procedure for asymmetric transfer hydrogenation of α,α-disubstituted ketones:

A mixture of catalyst (1 mol%) in FA:TEA (5:2) (0.15 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, ketone (0.3 mmol) was added and stirred at 28-45 ^{o}C for 9-47 h under an inert atmosphere. The completion of the reaction was confirmed by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol. The crude compound was purified by flash column chromatography.

Spiro[4,5]dec-2-ene-6,10-diol (323a).

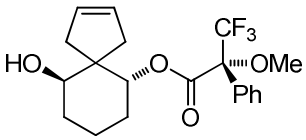


This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (7.56 mg, 0.0122 mmol, 2 mol%) in FA:TEA (5:2) (0.610 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, spiro[4,5]dec-2-ene-6,10-dione **312** (0.100 g, 0.610 mmol) was added and the mixture was stirred at 28 ^{o}C for 21 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol spiro[4,5]dec-2-ene-6,10-diol **323a** as a white solid (0.080 g, 0.476 mmol, 78%). Mp 98-100 ^{o}C; $[\alpha]_D^{20}$ = -63.0 (*c* 0.197 in $CHCl_3$); ν_{max} 3331, 2940, 2919, 2852, 1455, 1404, 1288, 1257, 1093, 1062, 1049, 959, 689 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.67 (2H, m, -C*H*=C*H*-), 3.83 (1H, d, *J* 2.4, -C*H*OH), 3.82 (1H, d, *J* 3.0, -C*H*OH), 2.60 (2H, d, *J* 15.0, -C*H*H-CH=CH-C*H*H-), 2.20 (2H, d, *J* 15.0, -CH*H*-CH=CH-CH*H*-), 1.72-1.50 (8H, m, -(CH_2)$_3$-2 x -O*H*); δc (75 MHz, $CDCl_3$) 129.66(2C), 73.95(2C), 38.89(2C), 30.14(2C), 18.47; m/z ESI-MS $[M+Na]^+$ 191.1; HRMS found 191.1039 ($C_{10}H_{16}O_2Na$ requires 191.1043, error = 1.7 ppm); the enantiomeric excess was determined by Chiral GC of the acetate derivative (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 150 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 39.133 min (minor enantiomer), 40.447 min (major enantiomer), %ee = 99%.

$NaBH_4$ reduction did not work in an attempt to prepare a racemic standard. The enantiomer was prepared by using (1*S*,2*S*) 3C-tethered-Ru complex.

Mosher's ester of (*R*,*R*)-spiro[4,5]dec-2-ene-6,10-diol (330a).



To a solution of (*R*,*R*)-spiro[4,5]dec-2-ene-6,10-diol **323a** (5 mg, 0.0298 mmol) in dry DCM (2 mL) was added TEA (0.014mL, 0.1044 mmol, 3.5 eq) and DMAP (1.0 mg). To the solution was added (*S*)-(+)-MTPA-Cl (0.014 mL, 0.0745 mmol, 2.5 eq) at 0 ^{o}C. The resulting solution was stirred at 22-23 ^{o}C for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: EtOAc (95:5) to give mono ester compound as an oil (7 mg, 0.0182 mmol,43%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^2 = 1.75-1.34 (6H, m, -(CH_2)$_3$-, -OH); L^3 = 2.67-2.59 (1H, m, -C*H*H-CH=CH-CHH-), 2.43-2.22 (2H, d, *J* 15.6, -CHH-CH=CH-CH_2-), 2.13-2.04 (1H, m, -CH*H*-CH=CH-CHH-).

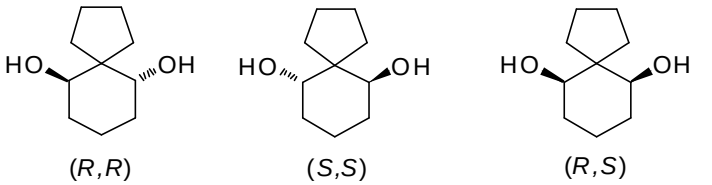
Mosher's ester of (*S*,*S*)-spiro[4,5]dec-2-ene-6,10-diol (330b).

The compound was prepared similarly as described for the Mosher's ester of (*R*,*R*)-spiro[4,5]dec-2-ene-6,10-diol.

^{1}H-NMR (key peaks) L^3 = 1.79-1.47 (6H, m, -(CH_2)$_3$-); L^2 = 2.64-2.56 (1H, m, -C*H*H-CH=CH-CHH-), 2.38-2.16 (2H, d, *J* 15.6, -CHH-CH=CH-CH_2-), 2.09-2.01 (1H, m, -CH*H*-CH=CH-CHH-).

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.1.

(*R*,*R*)-Spiro[4,5]decane-6,10-diol (324a).



(*R*,*R*) (*S*,*S*) (*R*,*S*)

Trans diastereomer *Cis* diastereomer

This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (7.5 mg, 0.0120 mmol, 2 mol%) in FA:TEA (5:2) (0.602 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, spiro[4,5]decane-6,10-dione **316** (0.100 g, 0.602 mmol) was added and stirred at 45 ^{o}C for 46 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: ethyl acetate (1:1) to ethyl acetate. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure *cis* alcohol **324c** as white solid (0.055 g, 0.323 mmol, 53%) and *trans* alcohol **324a** as white solid (0.025 g, 0.147 mmol, 24%). The ratio of *cis:trans* was calculated using crude ^{1}H-NMR spectrum to be 65: 35. The diastereomeric ratio and enantiomeric excess were determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 140 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 64.537 min (minor enantiomer, *trans*),

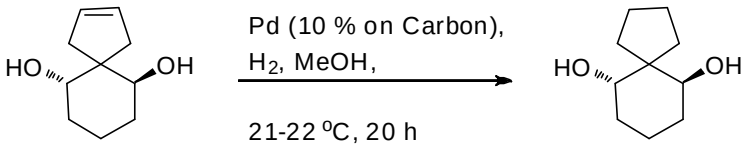
67.033 min (major enantiomer, *trans*), 68.363 min (*cis* diastereomer), dr = 65: 35 (*cis*:*trans*) %ee = 99%. GC quoted is of mixture prior to separation of *cis* and *trans* isomers. The ee of the *trans* isomer after separation was unchanged. The combination of ee and dr observed suggests that the second reduction is probably substrate controlled rather than catalyst controlled.

Cis diastereomer **324c**: Mp 94-95 ^{o}C; ν_{max} 3276, 2953, 2928, 2862, 1449, 1349, 1334, 1025, 1009, 955, 900 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.56 (2H, br s, -C*H*OH), 2.79 (2H, br s, -O*H*), 2.00-1.88 (1H, m, -CH_2-C*H*H-CH_2-), 1.81 (2H, t, *J* 7.5, -C*H*$_2$-(CH_2)$_2$-CH_2-), 1.73-1.66 (4H, m, -C*H*$_2$-CH_2-C*H*$_2$-), 1.64-1.55 (4H, m, -CH_2-(C*H*$_2$)$_2$-CH_2-), 1.42 (2H, t, *J* 7.5, -CH_2-(CH_2)$_2$-C*H*$_2$-), 1.38-1.32 (1H, m, -CH_2-C*H*H-CH_2-), δc (75 MHz, $CDCl_3$) 75.28(2C), 34.69, 32.33, 30.02(2C), 25.94, 25.44, 14.47; m/z ESI-MS $[M+Na]^+$ 193.1; HRMS found 193.1201 ($C_{10}H_{18}O_2Na$ requires 193.1199, error = -1.2 ppm);

Trans diastereomer **324a**: Mp 114-115 ^{o}C; $[\alpha]_D^{26}$ = -56.3 (*c* 0.175 in $CHCl_3$); ν_{max} 3327, 2939, 2865, 1443, 1392, 1273, 1050, 980, 957, 891, 878 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.75 (2H, dd, *J* 9.0, 3.0, -C*H*OH), 1.80-1.41 (16H, m, 14H of -C*H*$_2$-, 2H of -O*H*); δc (75 MHz, $CDCl_3$) 73.68(2C), 31.73, 30.66(2C), 26.79(2C), 18.66(2C); m/z ESI-MS $[M+Na]^+$ 193.1; HRMS found 193.1199 ($C_{10}H_{18}O_2Na$ requires 193.1199, error = 0.0 ppm); the enantiomeric excess was determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 140 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 65.230 min (minor enantiomer), 69.927 min (major enantiomer), %ee = 99%.

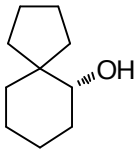
The racemic standard was prepared by $NaBH_4$ reduction. The retention times of the peaks in the GC of the diacetates of the crude product correlated with those of the *cis* and *trans* products after separation.

(*S*,*S*)-Spiro[4,5]decane-6,10-diol (323b) by Pd/C hydrogenation of (*S*,*S*)-spiro[4,5]dec-2-ene-6,10-diol (324b) to confirm that both were of same configuration (*S*).



A solution of (*S*,*S*)-spiro[4,5]dec-2-ene-6,10-diol (99% ee) **323b** (10 mg, 0.060 mmol) in dry methanol (2 mL) containing Pd/C (10 % on carbon) (6.39 mg) under atmospheric pressure of hydrogen at 21-22 ^{o}C was stirred for 22 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator to give (*S*,*S*)-spiro[4,5]decane-6,10-diol **324b** (9 mg, 0.053 mmol, 88%). the enantiomeric excess was determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 140 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 64.553 min (major enantiomer), 66.880 min (minor enantiomer), %ee = 99%.

Spiro[4,5]decane-6-ol (325a).

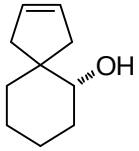


The racemic compound is known.[268]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (4.08 mg, 0.0066 mmol, 1 mol%) in FA:TEA (5:2) (0.329 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, spiro[4,5]decane-6-one **320** (0.100 g, 0.658 mmol) was added and stirred at 28 ^{o}C for 22 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **325a** as a white solid (0.095 g, 0.616 mmol, 93%). Mp 32-34 ^{o}C; $[\alpha]_D^{26}$ = -14.1 (*c* 0.500 in $CHCl_3$);ν_{max} 3284, 2927, 2857, 1447, 1342, 1139, 1065, 1050, 981, 892, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.45-3.42 (1H, m, -C*H*OH-), 1.75-1.15 (17H, m, 16H of -CH_2-, 1H of -OH); δc (75 MHz, $CDCl_3$) 75.75, 36.82, 35.75, 31.81, 25.78, 25.47, 22.93, 22.52; m/z ESI-MS $[M+Na]^+$ 177.2; HRMS found 177.1255 ($C_{10}H_{18}ONa$ requires 177.1250, error = -2.6 ppm); the enantiomeric excess was determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 115 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 39.067 min (minor enantiomer), 40.613 min (major enantiomer), %ee = 71%. The spectroscopic data were in agreement with literature values. [268]

$NaBH_4$ reduction failed in an attempt to prepare racemic standard. The opposite enantiomer was prepared by using (1*S*,2*S*) 3C-tethered-Ru complex for the GC comparison.

Spiro[4,5]dec-2-en-6-ol (326a).

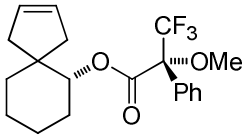


This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (4.13 mg, 0.00667 mmol, 1 mol%) in FA:TEA (5:2) (0.333 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, spiro[4,5]dec-2-en-6-one **321** (0.100 g, 0.667 mmol) was added and stirred at 28 ^{o}C for 18 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **326a** as a white solid (0.091 g, 0.598 mmol, 89%). $[\alpha]_D^{30}$ = -12.59 (*c* 0.975 in $CHCl_3$); ν_{max} 3389, 3050, 2926, 2857, 1622, 1449, 1350, 1271, 1136, 1094, 1060, 1034, 988, 940, 844, 801, 665 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.54 (2H, s, -C*H*=C*H*-), 3.51-3.48 (1H, m, -C*H*OH), 2.48 (1H, d, *J* 18.0, -C*H*H-CH=CH-CHH-), 2.46 (1H, d, *J* 18.0, -C*H*H-CH=CH-CHH-), 2.11 (1H, d, *J* 18.0, -CHH-CH=CH-C*H*H-), 2.05 (1H, d, *J* 18.0, -CH*H*-CH=CH-CHH-), 1.79-1.64 (3H, m, -CH_2-CHOH), 1.48-1.25 (6H, m, -(CH_2)$_3$-); δc (75 MHz, $CDCl_3$) 129.77, 128.97, 76.18, 46.80, 44.47, 38.06, 37.01 31.37, 23.53, 22.35; m/z ESI-MS $[M+Na]^+$ 177.2; HRMS found 175.1093 ($C_{10}H_{16}ONa$ requires 175.1093, error = 0.0 ppm); the enantiomeric excess was determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 115 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 34.573 min (minor enantiomer), 35.603 min (major enantiomer), %ee = 96%.

$NaBH_4$ reduction failed in an attempt to prepare racemic standard. The opposite enantiomer was prepared by using (1*S*,2*S*) 3C-tethered-Ru complex for the GC comparison.

Mosher's ester of (*R*) spiro[4,5]dec-2-en-6-ol (331a).



To a solution of (*R*) spiro[4,5]dec-2-en-6-ol **326a** (5 mg, 0.0329 mmol) in dry DCM (2 mL) was added TEA (0.016mL, 0.1151 mmol, 3.5 eq) and DMAP (1.0 mg). To the solution was added (*S*)-(+)-MTPA-Cl (0.015 mL, 0.0823 mmol, 2.5 eq) at 0 ^{o}C. The resulting solution was stirred at 22-23 ^{o}C for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: EtOAc (95:5) to give mono ester compound as an oil (6 mg, 0.0163mmol, 49%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^{2} = 1.81-1.72 (1H, m, -C*H*H-CHOH); L^{3} = 5.59-5.52 (2H, m, -C*H*=C*H*-), 2.43-2.36 (1H, m, -C*H*H-CH=CH-CHH-), 2.32-2.25 (1H, d, *J* 15.6, -CHH-CH=CH-C*H*H-), 2.20-2.14 (1H, m, -CHH-CH=CH-CH*H*-), 2.09-2.01 (1H, m, -CH*H*-CH=CH-CHH-).

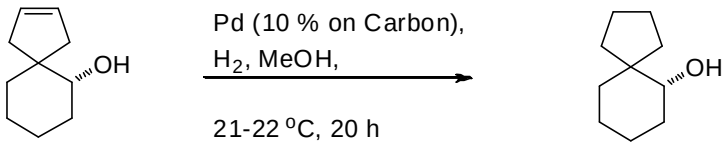
Mosher's ester of (*S*) spiro[4,5]dec-2-en-6-ol (331b).

The compound was prepared similarly as described for the Mosher's ester of (*R*) spiro[4,5]dec-2-en-6-ol (**326b**).

^{1}H-NMR (key peaks) L^{3} = 1.89-1.80 (1H, m, -C*H*H-CHOH); L^{2} = 5.52-5.43 (2H, m, -C*H*=C*H*-), 2.36-2.29 (1H, m, -C*H*H-CH=CH-CHH-), 2.26-2.17 (1H, d, *J* 15.6, -CHH-CH=CH-C*H*H-), 2.16-2.07 (1H, m, -CHH-CH=CH-CH*H*-), 2.03-1.95 (1H, m, -CH*H*-CH=CH-CHH-).

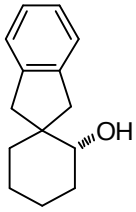
The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245]

Spiro[4,5]decane-6-ol (325a) by Pd/C hydrogenation of (*R*) spiro[4,5]dec-2-en-6-ol (326a) to confirm that both were of the same configuration.



A solution of (*R*) spiro[4,5]dec-2-en-6-ol **326a** (96% ee) (0.010 g, 0.066 mmol) in dry methanol (2 mL) containing added Pd/C (10 % on carbon) (7 mg) under atmospheric pressure of hydrogen at 21-22 ^{o}C, was stirred for 20 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator to give spiro[4,5]decane-6-ol **325a** (0.009 g, 0.058 mmol, 88%). The enantiomeric excess was determined by Chiral GC for acetate derivative GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 115 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 39.010 min (minor enantiomer), 39.933 min (major enantiomer), %ee = 96%.

1',3'-Dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-ol (327a).



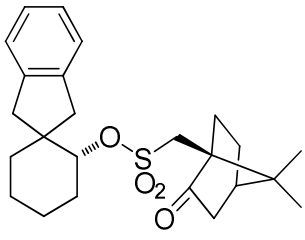
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.1 mg, 0.005 mmol, 1 mol%) in FA:TEA (5:2) (0.250 mL) was stirred at 28 ^{o}C under an inert atmosphere

in a Schlenk tube. To this, 1',3'-dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-one **322** (0.100 g, 0.500 mmol) was added and the solution was stirred at 28 ^{o}C for 22 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane:EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **327a** as a colourless oil (0.095 g, 0.570 mmol, 94%). $[\alpha]_D^{26}$ = -6.4 (*c* 0.250 in $CHCl_3$); ν_{max} 3391, 3021, 2926, 2857, 1697, 1484, 1448, 1300, 1222, 1060, 1029, 751, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19-7.10 (4H, m, -CH of -C_6H_4-), 3.65-3.62 (1H, m, -C*H*OH-), 3.12 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 3.07 (1H, d, *J* 15.0, -CHH-C_6H_4-C*H*H-), 2.71 (1H, d, *J* 18.0, -CH*H*-C_6H_4-CHH-), 2.66 (1H, d, *J* 15.0, -CHH-C_6H_4- CH*H*-), 1.83-1.66 (3H, m, -CH_2-), 1.57-1.25 (6H, m, -CH_2-, -O*H*); δc (75 MHz, $CDCl_3$) 142.66, 142.17, 126.14, 126.08, 124.76, 124.59, 75.27, 48.38, 43.35, 38.47, 35.22, 31.55, 23.01, 22.18; m/z ESI-MS $[M+Na]^+$ 225.2; HRMS found 225.1250 ($C_{14}H_{18}ONa$ requires 225.1250, error = -0.4 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 90:10, 0.50mL/min, 254 nM, 24 ^{o}C) R_t (min) = 14.014 (major enantiomer), 15.715 min (minor enantiomer), %ee = 93%.

The racemic standard was prepared by $LiAlH_4$ reduction.

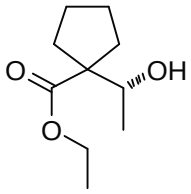
(1*S*)-(+)-10-camphorsulfonyl ester derivative of 1',3'-dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-ol (332).



To a solution of 1',3'-dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-one **327a** (100 mg, 0.495 mmol) in dry DCM (5 mL) was added TEA (0.172 mL, 1.238 mmol, 2.5 eq) and DMAP (1.2 mg, 0.02 eq). To the solution was added (*S*)-(+)-10-camphorsulfonyl chloride (0.186 g, 0.742 mmol, 1.5 eq) at 0 ^{o}C. The resulting solution was stirred at 22-23 ^{o}C overnight. The completion of the reaction was checked by TLC. The reaction mixture was diluted with water (15 mL) followed by extraction with DCM (2 x 15 mL). The combined organic layers were washed with 1 M HCl (2 x 10 mL), sat. $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane:EtOAc (84:16) to give compound **332** as oil (0.100 g, 0.240 mmol, 48%). The oil converted into a solid on standing. The solid was recrystallised from n-pentane:diethyl ether to give crystals for X-ray analysis. Mp 118-120 ^{o}C; $[\alpha]_D^{21}$ = + 15.51 (*c* 0.290 in $CHCl_3$); ν_{max} 2945, 1741, 1486, 1393, 1347, 1280, 1165, 941, 900, 872, 736 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.18-7.08 (4H, m, -CH of -C_6H_4-), 3.65-3.62 (1H, dd, *J* 9.0, 3.0, -C*H*OH-), 3.49 (1H, d, *J* 15.0, -SO_2-C*H*H-), 3.14 (1H, d, *J* 15.0, -C*H*H-C_6H_4-CHH-), 3.10 (1H, d, *J* 18.0, -CHH-C_6H_4-CH*H*-), 2.86 (1H, d, *J* 15.0, -SO_2-CH*H*-), 2.77 (1H, d, *J* 18.0, -CHH-C_6H_4-CH*H*-), 2.75 (1H, d, *J* 15.0, -CH*H*-C_6H_4- CHH-), 2.44-2.31 (2H, m, Cam -CH_2), 2.07 (1H, t, *J* 4.5, Cam -CH_2), 2.02-1.83 (4H, m, -C*H*$_2$-$CHOSO_2$-, Cam -CH_2), 1.80-1.70 (2H, m, -C*H*$_2$-CH_2-$CHOSO_2$-), 1.55-1.30 (6H, m, 4H of -C-C*H*$_2$-C*H*$_2$-, 2H of Cam -CH_2), 1.05 (3H, s, Cam -CH_3), 0.8 (3H, s, Cam -CH_3); δc (75 MHz, $CDCl_3$) 214.27, 141.84, 141.46, 126.28, 126.22, 124.66, 124.64, 86.29, 57.93, 48.29, 47.82, 47.52, 43.27, 42.69, 42.43, 39.80, 35.30, 29.88, 26.85, 24.77, 22.70, 21.65, 19.86, 19.66; m/z ESI-MS $[M+Na]^+$ 439.1; HRMS

found 439.1923 ($C_{24}H_{32}O_4SNa$ requires 439.1914, error = -2.2 ppm). The X-ray Structure was obtained (more details in Appendix 5.1.4).

Ethyl 1-(1-hydroxyethyl)cyclopentanecarboxylate (341a).



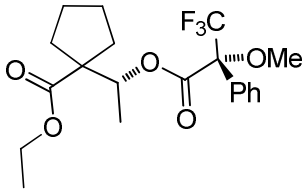
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.4 mg, 0.00543 mmol, 1 mol%) in FA:TEA (5:2) (0.270 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, ethyl 1-acetylcyclopentanecarboxylate **334** (0.100 g, 0.543 mmol) was added and the solution was stirred at 30 ^{o}C for 47 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **341a** as a colourless oil (0.095 g, 0.510 mmol, 94%). $[\alpha]_D^{28}$ = +6.2 (*c* 0.335 in $CHCl_3$); ν_{max} 3448, 2956, 2873, 1711, 1622, 1449, 1369, 1264, 1233, 1172, 1094, 1025, 897 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.19 (2H, q, *J* 7.0, -OC*H*$_2$CH$_3$), 3.77-3.71 (1H, m, -C*H*OH), 2.92 (1H, br s, -OH), 2.17-2.08 (1H, m, -C*H*$_2$-), 2.00-1.95 (1H, m, -C*H*$_2$-), 1.92-1.80 (1H, m, -C*H*$_2$-), 1.73-1.59 (4H, m, -C*H*$_2$-CH$_2$-,), 1.52-1.42 (1H, m, -C*H*$_2$-), 1.28 (3H, t, *J* 7.0, -OCH$_2$C*H*$_3$), 1.16 (3H, d, *J* 6.0, -C*H*$_3$); δc (75 MHz, $CDCl_3$) 72.63, 60.67, 58.84, 34.27, 32.79, 26.02, 25.59, 19.49, 14.19; m/z ESI-MS $[M+Na]^+$ 209.2; HRMS found 209.1152 ($C_{10}H_{18}O_3Na$ requires 209.1148, error = -1.7 ppm); the enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column,

Oven temperature 140 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 12.903 min (minor enantiomer), 13.263 min (major enantiomer), %ee = 61%.

$NaBH_4$ reduction failed in an attempt to prepare a racemic standard. The enantiomer was prepared by using (1*S*,2*S*) 3C-tethered-Ru complex.

Mosher's ester of ethyl (*R*) 1-(1-hydroxyethyl)cyclopentanecarboxylate (345a).



To a solution of ethyl (*R*) 1-(1-hydroxyethyl)cyclopentanecarboxylate **341a** (5 mg, 0.0268 mmol) in dry DCM (2 mL) was added TEA (0.0075 mL, 0.0536 mmol, 2.0 eq) and DMAP (1 mg). To the solution was added (*S*)-(+)-MTPA-Cl (0.0063 mL, 0.0034 mmol, 1.25 eq) at 0 ^{o}C. The resulting solution was stirred at 22-23 ^{o}C for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane:ethyl acetate (90:10) to give the product as an oil (5 mg, 0.0124 mmol, 46%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) of Mosher's ester of alcohol from (1*R*,2*R*) 3C-tethered-Ru complex **181.**

L^2= 1.24 (3H, d, *J* 6.0, -CH_3); L^3=1.63-1.55 (8H, m, -$(CH_2)_4$-)

Mosher's ester of ethyl (*S*) 1-(1-hydroxyethyl)cyclopentanecarboxylate(345b).

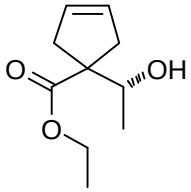
The compound was prepared by the same method as that described for the Mosher's ester of ethyl (*R*) 1-(1-hydroxyethyl)cyclopentanecarboxylate (**345a**).

^{1}H-NMR (key peaks) of Mosher's ester of alcohol from (1*S*,2*S*) 3C-tethered-Ru complex **181**.

L^3= 1.31 (3H, d, *J* 6.0, -C*H*$_3$); L^2=1.60-1.49 (8H, m, -(CH$_2$)$_4$-)

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.2.

Ethyl 1-(1-hydroxyethyl)cyclopent-3-ene-1-carboxylate (342a).



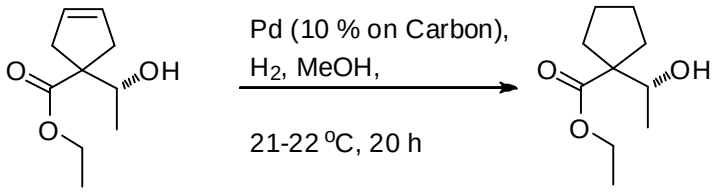
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (1.7 mg, 0.00275 mmol, 1 mol%) in FA:TEA (5:2) (0.138 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, ethyl 1-acetylcyclopent-3-enecarboxylate **336** (0.050 g, 0.275 mmol) was added and the solution was stirred at 28 ^{o}C for 30 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.050 g). The crude compound was purified by flash column chromatography to give pure alcohol **342a** as a colourless oil (0.045 g, 0.244 mmol, 89%). $[\alpha]_D^{26}$ = +31.27 (*c* 0.275 in CHCl$_3$); ν_{max} 3447, 2979, 2934, 1713, 1446, 1368, 1264, 1210, 1094, 1041, 947, 906, 672 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 5.68-5.63 (1H, m, -C*H*=CH-), 5.61-5.56 (1H, m, -CH=C*H*-), 4.20 (2H, q, *J* 7.0, -OC*H*$_2$CH$_3$), 3.95 (1H, m, -C*H*OH), 2.89-2.71 (3H, m,

-C*H*H-CH=CH-CH_2-), 2.60-2.45 (2H, m, -CH*H*-, -O*H*), 1.28 (3H, t, *J* 7.0, -OCH_2CH_3), 1.12 (3H, d, *J* 6.0, -CH_3); δc (75 MHz, $CDCl_3$) 177.36, 129.16, 128.00, 71.47, 60.95, 56.81, 40.45, 38.35, 18.05, 14.16; m/z ESI-MS $[M+Na]^+$ 207.1; HRMS found 207.0993 ($C_{10}H_{16}O_3Na$ requires 207.0992, error = -0.6 ppm); The enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 115 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Hydrogen, Pressure 15 psi) R_t (min) = 25.412 min (minor enantiomer), 26.335 min (major enantiomer), %ee = 92%.

$NaBH_4$ reduction failed in an attempt to prepare a racemic standard. The enantiomer was prepared by using (1*S*,2*S*) 3C-tethered-Ru complex. The products were combined to produce a racemic standard.

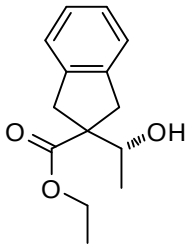
(*R*)-Ethyl 1-(1-hydroxyethyl)cyclopentanecarboxylate (341a) by Pd/C hydrogenation of ethyl 1-(1-hydroxyethyl)cyclopent-3-ene-1-carboxylate (342a) to confirm that both were of same configuration (*R*).



A solution of ethyl 1-(1-hydroxyethyl)cyclopent-3-ene-1-carboxylate **342a** (92% ee) (0.025 g, 0.136 mmol) in dry methanol (2 mL) containing Pd/C (10 % on carbon) (14.48 mg) under atmospheric pressure of hydrogen at 21-22 ^oC was stirred for 20 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator to give ethyl 1-(1-hydroxyethyl)cyclopentanecarboxylate **341a** (0.023 g, 0.123 mmol, 91%). The enantiomeric excess was established by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 140 ^oC,

Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 12.717 min (minor enantiomer), 12.923 min (major enantiomer), %ee = 92%.

Ethyl 2-(1-hydroxyethyl)-2,3-dihydro1H-indene-2-carboxylate (343a).



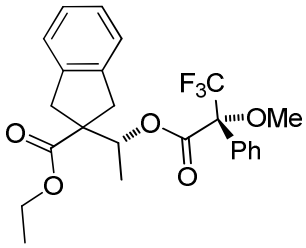
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (2.7 mg, 0.00431 mmol, 1 mol%) in FA:TEA (5:2) (0.216 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, ethyl 2-acetyl-2,3-dihydro-1H-indene-2-carboxylate **337** (0.100 g, 0.431 mmol) was added and stirred at 28 ^{o}C for 17 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **343a** as a colourless oil (0.095 g, 0.406 mmol, 94%). $[\alpha]_D^{26}$ = +21.8 (*c* 0.415 in $CHCl_3$); ν_{max} 3450, 2958, 1715, 1486, 1460, 1368, 1282, 1201, 1178, 1095, 1043, 902, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.20-7.13 (4H, m, -C*H* of -C_6H_4-), 4.20 (2H, q, *J* 7.2, -O*CH*$_2$CH$_3$), 4.02-3.95 (1H, m, -C*H*OH), 3.47 (1H, d, *J* 18, -C*H*H-C_6H_4-CH_2-), 3.39 (1H, d, *J* 16.5, -CH_2-C_6H_4-C*H*H-), 3.20 (1H, d, *J* 18, -CH_2-C_6H_4-CH*H*-), 3.05 (1H, d, *J* 16.5, - CH*H*-C_6H_4-CH_2-), 2.79 (1H, d, *J* 6.0, -O*H*), 1.25 (3H, t, *J* 7.2, -OCH_2C*H*$_3$), 1.11 (3H, d, *J* 6.0, -C*H*$_3$); δc (75 MHz, $CDCl_3$) 176.65, 141.61, 140.70,

126.65, 126.59, 124.27, 124.11, 71.73, 61.14, 58.43, 40.27, 38.24, 18.70, 14.15; m/z ESI-MS $[M+Na]^+$ 257.2; HRMS found 257.1152 ($C_{14}H_{18}O_3Na$ requires 257.1148, error = -1.4 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50mL/min, 254 nM, 26 ^oC) R_t (min) = 21.654 (major enantiomer), 23.337 min (minor enantiomer), %ee = 90%.

The racemic standard was prepared by $NaBH_4$ reduction.

Mosher's ester of ethyl (*R*)-2-(1-hydroxyethyl)-2,3-dihydro1H-indene-2-carboxylate (346a).



To a solution of ethyl 2-(1-hydroxyethyl)-2,3-dihydro1H-indene-2-carboxylate **343a** (39 mg, 0.167 mmol) in dry DCM (2 mL) was added TEA (0.046 mL, 0.334 mmol, 2.0 eq) and DMAP (2.0 mg, 0.1 eq). The solution was added (*S*)-(+)-MTPA-Cl (0.046 mL, 0.250 mmol, 1.5 eq) at 0 ^oC. The resulting solution was stirred at 21-22 ^oC for 5 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: EtOAc (95:5) to give an oil (50 mg, 0.111 mmol, 66%). $[\alpha]_D^{21}$ = + 48.03 (*c* 0.305 in $CHCl_3$); ν_{max} 2985, 1739, 1488, 1451, 1385, 1238, 1150, 1121, 1014, 858, 741, 715 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48-7.46 (2H, m, -CH of -C_6H_5), 7.39-7.32 (3H, m, -CH of -C_6H_5), 7.14-7.12 (4H, m, -CH of -C_6H_4-), 5.67-5.60 (1H, q, *J* 7.0, -C*H*OCO-), 4.19-4.04 (2H, m, -COOC*H*$_2$CH$_3$), 3.58 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 3.47 (3H, d, -OCH3), 3.43

(1H,d, *J* 15.0, -CHH-C_6H_4-C*H*H-), 3.10 (1H, d, *J* 18.0, -CHH-C_6H_4-CH*H*-), 3.03 (1H, d, *J* 15.0, -CH*H*-C_6H_4-CHH-), 1.20 (3H, t, *J* 9, -$COOCH_2CH_3$), 1.16 (3H, d, *J* 6.0, -$OCHCH_3$), δc (75 MHz, $CDCl_3$) 129.54, 128.34(2C), 127.39(2C), 126.86, 126.77, 124.16, 124.11, 76.61, 61.38, 57.04, 55.28, 39.33, 38.10, 15.27, 13.96; m/z ESI-MS $[M+Na]^+$ 473.1; HRMS found 473.1561 ($C_{24}H_{25}F_3O_5Na$ requires 473.1546, error = -3.1 ppm).

^{1}H-NMR (key peaks) L^2 = 1.16 (3H, d, *J* 6.0, -CH_3); L^3 = 3.58 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 3.43 (1H,d, *J* 15.0, -CH_2-C_6H_4-C*H*H-), 3.10 (1H, d, *J* 18.0, -CH_2-C_6H_4-CH*H*-), 3.03 (1H, d, *J* 15.0, -CH*H*-C_6H_4-CH_2-),

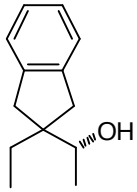
Mosher's ester of ethyl 2-(1-hydroxyethyl)-2,3-dihydro1H-indene-2-carboxylate racemic alcohol(346b).

The compound was prepared as described for the Mosher's ester of ethyl (*R*)-2-(1-hydroxyethyl)-2,3-dihydro1H-indene-2-carboxylate.

^{1}H-NMR (key peaks) L^3 = 1.26 (3H, d, *J* 6.0, -CH_3); L^2 = 3.54 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 3.38 (1H, d, *J* 15.0, -CH_2-C_6H_4-C*H*H-), 3.06 (1H, d, *J* 15.0, -CH_2-C_6H_4-CH*H*-), 2.99 (1H, d, *J* 15.0, - C*H*H-C_6H_4-CH_2-).

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.3.

(*R*) 1-(2-Ethyl-2,3-dihydro-1H-indene-2-yl)ethanol (344a).

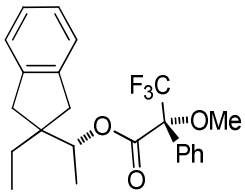


This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.3 mg, 0.00532 mmol, 1 mol%) in FA:TEA (5:2) (0.266 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, 1-(2-ethyl-2,3-dihydro-1H-inden-2-yl)ethanone **340** (0.100 g, 0.532 mmol) was added and stirred at 28 ^{o}C for 24 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: ethyl acetate (1:1) to ethyl acetate. The filtrate was concentrated to give crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **344a** as a colourless oil (0.090 g, 0.473 mmol, 89%). $[\alpha]_D^{28}$ = -3.18 (*c* 0.550 in $CHCl_3$); ν_{max} 3391, 3021, 2965, 2918, 1587, 1484, 1459, 1377, 1301, 1066, 982, 894, 788, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.16-7.09 (4H, m, -C*H* of -C_6H_4-), 3.87 (1H, q, *J* 6.0, -C*H*OH), 3.04 (1H, d, *J* 18, -C*H*H-C_6H_4-CH_2-), 2.98 (1H, d, *J* 18, -CH_2-C_6H_4-C*H*H-), 2.73 (1H, d, *J* 18, -CH_2-C_6H_4-CH*H*-), 2.69 (1H, d, *J* 18, - CH*H*-C_6H_4-CH_2-), 1.70-1.58 (1H, m, -C*H*HCH_3), 1.55-1.43 (1H, m, -CH*H*CH_3), 1.39 (1H, br s, -O*H*), 1.13 (3H, d, *J* 6.0, -CH_3), 0.83 (3H, t, *J* 7.5, -CH_2CH_3); δc (75 MHz, $CDCl_3$) 142.98, 142.78, 126.13(2C), 124.32, 124.21, 72.56, 50.50, 39.99(2C), 29.65, 18.63, 8.82; m/z ESI-MS $[M+Na]^+$ 213.1; HRMS found 253.1258 ($C_{13}H_{18}ONa$ requires 213.1250, error = -4.0 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50 mL/min, 254 nM, 26 ^{o}C) R_t (min) = 14.769 (major enantiomer), 16.783 min (minor enantiomer), %ee = 73%.

The racemic standard was prepared by $NaBH_4$ reduction.

Mosher's ester of (*R*) 1-(2-ethyl-2,3-dihydro-1H-indene-2-yl)ethanol (347a).



To a solution of (*R*) 1-(2-ethyl-2,3-dihydro1H-indene-2-yl)ethanol **344a** (5 mg, 0.0263 mmol) in dry DCM (1 mL) was added TEA (0.0073 mL, 0.0526 mmol, 2.0 eq) and DMAP (1 mg). The solution was added (*S*)-(+)-MTPA-Cl (0.0062 mL, 0.0329 mmol, 1.25 eq) at 0 ^{o}C. The resulting solution was stirred at 21-22 ^{o}C for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: ethyl acetate (90:10) to give the product as an oil (6 mg, 0.0148 mmol, 56%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^{2}= 1.22 (3H, d, *J* 6.0, -C*H*$_3$); L^{3}=2.94 (1H, d, *J* 12.0, -C*H*H-C_6H_4-CH_2-), 2.93 (1H,d, *J* 12.0, -CH_2-C_6H_4-C*H*H-), 2.74 (1H, d, *J* 12.0, -CH_2-C_6H_4-CH*H*-), 2.72 (1H, d, *J* 12.0, -CH*H*-C_6H_4-CH_2-).

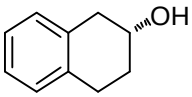
Mosher's ester of 1-(2-ethyl-2,3-dihydro-1H-indene-2-yl)ethanol racemic alcohol (347b).

The compound was prepared as described for the Mosher's ester of ethyl (*R*) 1-(2-ethyl-2,3-dihydro-1H-indene-2-yl)ethanol.

^{1}H-NMR (key peaks) L^{3}= 1.28 (3H, d, *J* 6.0, -C*H*$_3$); L^{2}=2.92 (1H, d, *J* 12.0, -C*H*H-C_6H_4-CH_2-), 2.85 (1H,d, *J* 12.0, -CH_2-C_6H_4-C*H*H-), 2.70 (1H, d, *J* 12.0, -CH_2-C_6H_4-CH*H*-), 2.67 (1H, d, *J* 12.0, -CH*H*-C_6H_4-CH_2-).

The relative positions of the L^{2} and L^{3} peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.4.

β-Tetralol (357a).



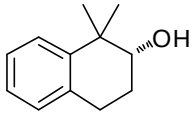
This is a known compound.[173,175]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (2.1 mg, 0.00342 mmol, 1 mol%) in FA:TEA (5:2) (0.171 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, β-tetralone **348** (0.050 g, 0.342 mmol) was added and the solution was stirred at 28 ^{o}C for 30 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.050 g). The crude compound was purified by flash column chromatography to give pure alcohol **357a** as a light brown oil (0.045 g, 0.304 mmol, 88%). $[\alpha]_D^{23}$ = +52.7 (*c* 0.370 in $CHCl_3$) [lit. value $[\alpha]_D^{23}$ = -51.4 (*c* 0.70 in $CHCl_3$) 82% ee (*S*)][173]; ν_{max} 3338, 3018, 2925, 2842, 1495, 1452, 1437, 1360, 1290, 1231, 1111, 1037, 962, 741 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.14-7.06 (4H, m, -CH of -C_6H_4-), 4.20-4.11 (1H, m, -C*H*OH), 3.12-3.06 (1H, dd, *J* 15.0, 3.0, -C_6H_4-CH*H*CHOH), 3.01-2.84 (2H, m, -CH_2-C_6H_4-), 2.81-2.73 (1H, dd, *J* 18.0, 6.0, -C_6H_4-CH_2CHOH), 2.11-2.01 (1H, m, -C*H*HCHOH), 1.88-1.76 (1H, m, -CH*H*CHOH), 1.71 (1H, br s, -O*H*); δc (75 MHz, $CDCl_3$) 135.62, 134.20, 129.50, 128.58, 125.96, 125.84, 67.23, 38.38, 31.47, 26.95; m/z ESI-MS $[M+Na]^+$ 171.2; HRMS found 171.0777 ($C_{10}H_{12}ONa$ requires 171.0780, error = 2.1 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 95:5, 0.50mL/min, 254 nM, 19 ^{o}C) R_t (min) = 17.390 (minor

enantiomer, *S*), 18.791 min (major enantiomer, *R*), %ee = 88%. The spectroscopic data were in agreement with literature values. [173,175]

The racemic standard was prepared by $NaBH_4$ reduction.

1,1-Dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (358a).



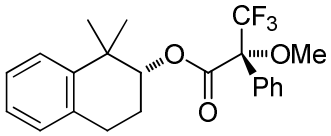
The racemic compound is known.[269]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (1.8 mg, 0.00287 mmol, 1 mol%) in FA:TEA (5:2) (0.150 mL) was stirred at 28 ^oC under an inert atmosphere in a Schlenk tube. To this, 1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one **349** (0.050 g, 0.287 mmol) was added and the solution was stirred at 28 ^oC for 9 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane:EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.050 g). The crude compound was purified by flash column chromatography to give pure alcohol **358a** as a colourless oil (0.045 g, 0.255 mmol, 89%). $[\alpha]_D^{21}$ = +23.48 (*c* 0.445 in $CHCl_3$); ν_{max} 3370, 2967, 2937, 1489, 1446, 1383, 1361, 1286, 1038, 758, 727 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.33 (1H, m, -C*H* of -C_6H_4-,), 7.20-7.05 (3H, m, -C*H* of -C_6H_4-), 3.77 (1H, dd, *J* 9.0, 3.0, -C*H*OH-), 3.01-2.80 (2H, m, C_6H_4-CH_2-), 2.13 (1H, br s, -O*H*), 2.08-1.87 (2H, m, -CH_2-CHOH-), 1.34 (3H, s, -CH_3), 1.29 (3H, br s, -CH_3); δc (75 MHz, $CDCl_3$) 144.17, 134.46, 128.71, 126.85, 126.16, 125.66, 75.60, 39.08, 28.93, 26.98, 26.78, 24.98; m/z ESI-MS $[M+Na]^+$ 199.2; HRMS found 199.1089 ($C_{12}H_{16}ONa$ requires 199.1093, error = 2.2 ppm); the enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 150

^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 28.643 min (minor enantiomer), 28.820 min (major enantiomer), %ee = 94%. The spectroscopic data were in agreement with literature values. [269]

The racemic standard was prepared by $NaBH_4$ reduction.

Mosher's ester of (*R*) 1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (364a).



To a solution of 1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol **358a** (5 mg, 0.0284 mmol) in dry DCM (2 mL) was added TEA (0.008 mL, 0.057 mmol, 2.0 eq) and DMAP (1 mg). The solution was added (*S*)-(+)-MTPA-Cl (0.0066 mL, 0.0355 mmol, 1.25 eq) at 0 ^{o}C. The resulting solution was stirred at 21-22 ^{o}C for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: ethyl acetate (90:10) to give the product as an oil (6 mg, 0.0153mmol, 53%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^2= 2.17-1.97 (2H, m, -C*H*$_2$-CHOH-); L^3= 1.33 (3H, s, -CH_3), 1.26 (3H, br s, -CH_3),

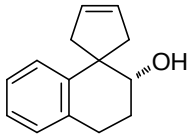
Mosher's ester of racemic 1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (364b).

The compound was prepared similarly as described for the Mosher's ester of (*R*) 1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol.

^{1}H-NMR (key peaks) L^3= 2.21-2.06 (2H, m, -C*H*$_2$-CHOH-); L^2= 1.27 (3H, s, -CH_3), 1.19 (3H, br s, -CH_3),

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.5.

3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol (359a).



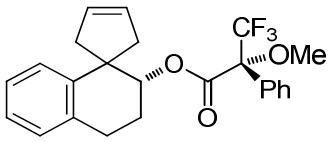
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.13 mg, 0.00505 mmol, 1 mol%) in FA:TEA (5:2) (0.250 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-one **351** (0.100 g, 0.505 mmol) was added and the solution was stirred at 28 ^{o}C for 20 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **359a** as a white solid (0.090 g, 0.450 mmol, 89%). Mp 84-86 ^{o}C; $[\alpha]_D^{21}$ = +38.8 (*c* 0.350 in $CHCl_3$); ν_{max} 3347, 3062, 2937, 2851, 1624, 1488, 14532, 1426, 1344, 1283, 1243, 1185, 1085, 1059, 946, 936, 923, 754, 732, 702, 668 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.24 (1H, m, -CH of -C_6H_4-), 7.17-7.03 (3H, m, -CH of -C_6H_4-), 5.79 (2H, m, -C*H*=C*H*-), 3.90 (1H, dd, *J* 9.0, 3.0, -C*H*OH), 3.02-2.76 (3H, m, -C*H*$_2$-C_6H_4- and -C*H*H-CH=CH-CH_2-), 2.73-2.67 (2H,

m, -CHH-CH=CH-CH_2-), 2.48-2.39 (1H, m, -CH_2-CH=CH-CH*H*-), 2.04-1.84 (2H, m, -CH_2-CHOH-), 1.67 (1H, br s, -O*H*); δc (75 MHz, $CDCl_3$) 145.70, 133.71, 130.17, 129.37, 128.38, 126.77, 126.70, 125.74, 75.05, 49.51, 48.38, 44.28, 27.92, 27.00; m/z ESI-MS $[M+Na]^+$ 223.2; HRMS found 223.1088 ($C_{14}H_{16}ONa$ requires 223.1093, error = 2.5 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 98:2, 0.50mL/min, 254 nM, 15 ^oC) R_t (min) = 30.385 (minor enantiomer), 34.728 min (major enantiomer), %ee = 99%.

The racemic standard was prepared by $NaBH_4$ reduction.

Mosher's ester of (*R*) 3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol (365a).



To a solution of 3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol **359a** (10 mg, 0.050 mmol) in dry DCM (2 mL) was added TEA (0.014 mL, 0.100 mmol, 2.0 eq) and DMAP (1 mg). The solution was added (*S*)-(+)-MTPA-Cl (0.014 mL, 0.075 mmol, 1.5 eq) at 0 ^oC. The resulting solution was stirred at 20-21 ^oC for 18 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane: EtOAc (95:5) to give the product as oil (8 mg, 0.0192mmol, 38%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^2= 2.11-1.93 (2H, m, -CH_2-CHOH-); L^3= 2.73-2.67 (2H, m, -CHH-CH=CH-CH_2-)

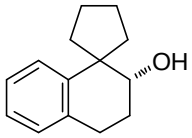
Mosher's ester of racemic 3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol (365b).

The compound was prepared similarly as described for the Mosher's ester of (*R*) 3',4'-Dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol.

^{1}H-NMR (key peaks) L^3= 2.17-2.09 (2H, m, -C*H*$_2$-CHOH-); L^2= 2.61-2.58 (2H, m, -CHH-CH=CH-C*H*$_2$-)

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.6.

(*R*)- 3',4'-Dihydro-2'H-spiro[cyclopentane-1,1'-naphthalene]-2'-ol (360a).



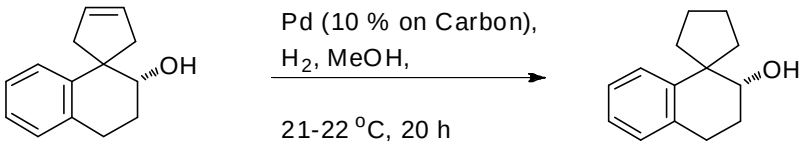
The racemic compound is known.[264]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.1 mg, 0.005 mmol, 1 mol%) in FA:TEA (5:2) (0.250 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, 3',4'-dihydro-spiro[cyclopentane-1,1'-[2H]-naphthalene]-2'-one **352** (0.100 g, 0.500 mmol) was added and the solution was stirred at 28 ^{o}C for 18 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane:EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **360a** as white solid (0.090 g, 0.445 mmol, 89%). Mp 72-74 ^{o}C; $[\alpha]_D^{21}$ = -34.66 (*c* 0.225 in $CHCl_3$); ν_{max} 3348, 3055, 3022, 2954, 2937, 2871, 1574,

1488, 1426, 1295, 1187, 1067, 945, 756, 709 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.24 (1H, m, -CH of -C_6H_4-), 7.18-7.04 (3H, m, -CH of -C_6H_4-), 3.80 (1H, dd, *J* 9.0, 3.0, -C*H*OH), 3.06-2.95 (1H, m, -C*H*H-C_6H_4-), 2.85-2.77 (1H, m, -CH*H*-C_6H_4-), 2.16-1.78 (10H, m, -CH_2-CHOH and-(CH_2)$_4$-), 1.55 (1H, br s, -O*H*); δc (75 MHz, $CDCl_3$) 144.87, 134.65, 128.54, 127.50, 126.27, 125.46, 74.38, 51.14, 41.83, 37.10, 27.53, 27.22, 26.67, 25.57; m/z ESI-MS $[M+Na]^+$ 225.2; HRMS found 225.1250 ($C_{14}H_{18}ONa$ requires 225.1250, error = -0.4 ppm); The enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 98:2, 0.50mL/min, 254 nM, 12 ^oC) R_t (min) = 30.979 (minor enantiomer), 33.814 min (major enantiomer), %ee = 99%.

The racemic standard was prepared by $NaBH_4$ reduction.

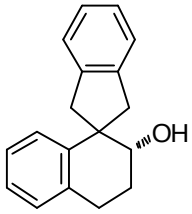
(*R*)- 3',4'-Dihydro-2'H-spiro[cyclopentane-1,1'-naphthalene]-2'-ol (360a) by Pd/C hydrogenation of 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol (359a) to confirm that both were of the same configuration.



A solution of 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol **359a** (99% ee) (0.010 g, 0.05 mmol) in dry methanol (2 mL) containing added Pd/C (10 % on carbon) (5 mg) under atmospheric pressure of hydrogen at 21-22 ^oC, was stirred for 20 h. The reaction mixture was filtered through Celite and the filtrate was concentrated on a rotary evaporator to give 3',4'-dihydro-2'H-spiro[cyclopentane-1,1'-naphthalene]-2'-ol **360a** (0.010 g, 0.049 mmol, 99%). The enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm,

hexane:IPA 98:2, 0.50mL/min, 254 nM, 12 ^{o}C) R_t (min) = 30.979 (minor enantiomer), 34.079 min (major enantiomer), %ee = 99%.

1,3,3',4'-Tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-2'-ol (361a).



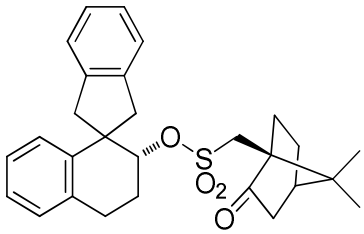
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (2.5 mg, 0.00403 mmol, 1 mol%) in FA:TEA (5:2) (0.200 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, 1,3,3',4'-tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-one **353** (0.100 g, 0.403 mmol) was added and the solution was stirred at 30 ^{o}C for 24 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **361a** as white solid (0.090 g, 0.360 mmol, 89%). Mp 90-92 ^{o}C; $[\alpha]_D^{21}$ = -40.71 (*c* 0.350 in $CHCl_3$); ν_{max} 3570, 2934, 2872, 2832, 1486, 1455, 1216, 1110, 1079, 995, 759, 751, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23-7.18 (4H, m, 4 -CH of -C_6H_4-), 7.10-7.05 (2H, m, 2-CH of -C_6H_4-), 7.03-6.97 (2H, m, 2-CH of -C_6H_4-), 4.06-3.96 (1H, m, -C*H*OH), 3.58 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 3.31 (1H, d, *J* 15.0, -CH_2-C_6H_4-C*H*H-), 3.16 (1H, d, *J* 15.0, -CHH-C_6H_4-CH*H*-), 3.11 (1H, d, *J* 18.0, -CH*H*-C_6H_4-CH_2), 3.08-3.00 (1H, m, -C*H*H-C_6H_4-), 2.95-2.84 (1H, m, -CH*H*-C_6H_4-), 2.14-1.95 (2H, m, -CH_2CHOH-), 1.64 (1H, br d, -OH); δc (75 MHz, $CDCl_3$) 144.19, 142.87, 142.06, 133.85, 128.70, 126.67,

126.52(2C), 126.47, 126.03, 124.38, 124.33, 74.37, 50.85, 47.36, 43.61, 27.67, 26.08; m/z ESI-MS $[M+Na]^+$ 273.2; HRMS found 273.1252 ($C_{18}H_{18}ONa$ requires 273.1250, error = -1.1 p); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 98:2, 0.50mL/min, 254 nM, 23 ^oC) R_t (min) = 52.365 (minor enantiomer), 54.326 min (major enantiomer), %ee = 99%.

The racemic standard was prepared by $NaBH_4$ reduction.

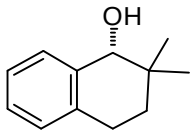
(1*S*)-(+)-10-camphorsulfonyl ester derivative 7 of 1,3,3',4'-tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-ol (366).



To a solution of 1,3,3',4'-tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-ol **361a** (50 mg, 0.200 mmol) in dry DCM (4 mL) was added TEA (0.055 mL, 0.400 mmol, 2.0 eq) and DMAP (0.5 mg, 0.02 eq). To the solution was added (*S*)-(+)-10-camphorsulfonyl chloride (0.075 g, 0.300 mmol, 1.5 eq) at 0 ^oC. The resulting solution was stirred at 21-22 ^oC for overnight. The completion of the reaction was checked by TLC. The reaction mixture was diluted with water (10 mL) followed by extraction with DCM (2 x 10 mL). The combined organic layers were washed with 1 M HCl (2 x 10 mL), sat. $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane:EtOAc (90:10) to give compound **366** as a colourless oil (0.060 g, 0.129 mmol, 64%). The oil converted into a solid on standing. The solid was recrystallised

from n-pentane: diethyl ether to give crystals for X-ray analysis. Mp 126-128 ^{o}C; $[\alpha]_D^{26}$ = + 5.93 (*c* 0.295 in $CHCl_3$); ν_{max} 2967, 2909, 1746, 1488, 1351, 1361, 1712, 1059, 905, 888, 828, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24-7.17 (4H, m, 4 -CH of -C_6H_4-), 7.10-7.07 (2H, m, 2-CH of -C_6H_4-), 7.03-6.98 (2H, m, 2-CH of -C_6H_4-), 5.16 (1H, dd, *J* 6.0, 3.0, -C*H*OH), 3.56 (1H, d, *J* 12.0, -C*H*H-C_6H_4-CHH-), 3.53 (1H, d, *J* 9.0, -SO_2-C*H*H-), 3.35 (1H, d, *J* 12.0, -CHH-C_6H_4-C*H*H-), 3.22 (1H, d, *J* 12.0, -CH-H-C_6H_4-CH*H*-), 3.19 (1H, d, *J* 12.0, -CH*H*-C_6H_4-CHH-), 3.15-3.07 (1H, m, -C*H*H-C_6H_4-), 2.99-2.94 (1H, m, -CH*H*-C_6H_4-), 2.93 (1H, d, *J* 9.0, -SO_2-CH*H*-), 2.43-2.17 (4H, m, -C*H*$_2$CHOSO$_2$-, Cam -CH_2), 2.05 (1H, t, *J* 3.0, Cam -CH_2), 1.99-1.90 (1H, m, Cam -CH_2), 1.87 (1H, d, *J* 12.0, Cam -CH_2), 1.51-1.44 (1H, m, Cam -CH_2), 1.34-1.28 (1H, m, Cam -CH_2), 1.03 (3H, s, Cam -CH_3), 0.82 (3H, s, Cam -CH_3); δc (75 MHz, $CDCl_3$) 214.13, 143.15, 142.24, 141.14, 133.28, 128.61, 126.87, 126.71, 126.65, 126.33, 125.91, 124.48, 124.49, 84.89, 57.92, 49.72, 48.36, 47.80, 47.68, 44.81, 42.70, 42.38, 26.81, 26.34, 25.98, 24.74, 19.80, 19.65; m/z ESI-MS $[M+Na]^+$ 487.0; HRMS found 487.1933 ($C_{28}H_{32}O_4SNa$ requires 487.1914, error = -3.6 ppm); The X-ray Structure was obtained (more details in Appendix 5.1.5).

(*R*)-2,2-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (362a).



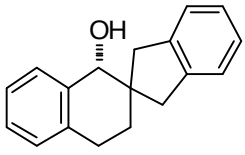
This compound is known.[270]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (3.56 mg, 0.00575 mmol, 1 mol%) in FA:TEA (5:2) (0.287 mL) was stirred at 28 ^{o}C under an inert atmosphere in a Schlenk tube. To this, 2,2-dimethyl-3,4-dihydronaphthalen-1(2H)-

one **355** (0.100 g, 0.575 mmol) was added and the solution was stirred at 45 ^{o}C for 49 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: ethyl acetate (1:1) to ethyl acetate. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **362a** as a colourless oil (0.090 g, 0.511 mmol, 89%). $[\alpha]_D^{30}$ = -20.2 (*c* 1.125 in $CHCl_3$) [lit. value $[\alpha]_D^{22}$ = -23.5 (*c* 3.37 in $CHCl_3$) (*R*)][271]; δ_H (300 MHz, $CDCl_3$) 7.47-7.41 (1H, m, -C*H* of -C_6H_4-,), 7.22-7.17 (2H, m, -C*H* of -C_6H_4-), 7.13-7.08 (1H, m, -C*H* of -C_6H_4-), 4.26 (1H, d, *J* 6.0, -C*H*OH-), 2.89-2.70 (2H, m, C_6H_4-CH_2-), 1.86-1.77 (1H, m, C_6H_4-CH_2-C*H*H-), 1.61-1.49 (2H, m, -O*H*, C_6H_4-CH_2-CH*H*-), 1.00 (3H, s, -CH_3), 0.98 (3H, s, -CH_3); δc (75 MHz, $CDCl_3$) 138.45, 135.87, 128.80, 128.73, 127.32, 126.12, 76.63, 33.83, 31.92, 25.93, 25.59, 22.53; m/z ESI-MS $[M+Na]^+$ 199.1; the enantiomeric excess by using Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 140 ^{o}C, Injection temperature 220 ^{o}C, Detection temperature 220 ^{o}C, Gas Hydrogen, Pressure 15 psi) R_t (min) = 29.423 min (major enantiomer), 29.917 min (major enantiomer), %ee = 98%. The spectroscopic data were in agreement with literature values. [269]

The racemic standard was prepared by $NaBH_4$ reduction.

Spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol, 1,3,3',4'-tetrahydro (363a).



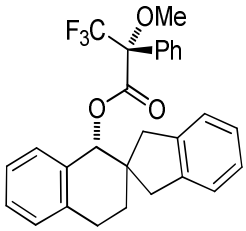
This is a novel compound.

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (2.5 mg, 0.00403 mmol, 1 mol%) in FA:TEA (5:2) (0.200 mL) was stirred at 28 ^{o}C under an inert atmosphere

in a Schlenk tube. To this, 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-one **356** (0.100 g, 0.403 mmol) was added and the solution was stirred at 45 ^{o}C for 24 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane: EtOAc (1:1) to EtOAc. The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give pure alcohol **363a** as white solid (0.085 g, 0.340 mmol, 84%). Mp 74-75 ^{o}C; $[\alpha]_D^{16}$ = +30.94 (*c* 0.265 in $CHCl_3$); ν_{max} 3565, 3020, 2903, 2841, 1484, 1450, 1382, 1262, 1176, 1103, 1031, 1008, 938, 794, 773, 736 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35-7.32 (1H, m, -CH of -C_6H_4-), 7.27-7.11 (7H, m, -CH of -C_6H_4-), 4.43 (1H, d, *J* 6.0, -C*H*OH-), 3.31 (1H, d, *J* 15.0, -C*H*H-C_6H_4-CHH-), 2.93-2.89 (2H, m, -CH_2-C*H*$_2$-C_6H_4-), 2.83 (1H, d, *J* 15.0, -CHH-C_6H_4-C*H*H-), 2.78 (1H, d, *J* 15.0, -CHH-C_6H_4-CH*H*-), 2.68 (1H, d, *J* 15.0, -CH*H*-C_6H_4-CHH-), 2.22-2.12 (1H, m, -C*H*$_2$-C-), 1.80-1.72 (1H, m, -C*H*$_2$-C-), 1.66 (1H, br d, -OH); δc (75 MHz, $CDCl_3$) 142.38, 142.04, 137.89, 136.06, 129.95, 129.10, 127.93, 126.35, 126.25, 126.20, 124.86, 124.67, 74.40, 46.98, 41.36, 40.67, 28.15, 26.30; m/z ESI-MS $[M+Na]^+$ 273.1; HRMS found 273.1254 ($C_{18}H_{18}ONa$ requires 273.1250, error = -1.6 ppm); the enantiomeric excess was determined by Chiral HPLC (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:IPA 90:10, 0.50mL/min, 254 nM, 12 ^{o}C) R_t (min) = 16.401 (major enantiomer), 22.026 min (minor enantiomer), %ee = 99%.

The racemic standard was prepared by $NaBH_4$ reduction.

Mosher's ester of (*R*) 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol 18 (369a).



To a solution of 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol **363a** (12 mg, 0.048 mmol) into dry DCM (2 mL) was added TEA (0.017 mL, 0.120 mmol, 2.5 eq) and DMAP (1 mg). The solution was added (*S*)-(+)-MTPA-Cl (0.014 mL, 0.072 mmol, 1.5 eq) at 0 ^{o}C. The resulting solution was stirred at 21-22 ^{o}C for 1.5 h. The completion of the reaction was checked by TLC. The reaction mixture was concentrated on a rotary evaporator to get oil. The oil was purified by flash column chromatography using hexane:EtOAc (95:5) to give the product as oil (8 mg, 0.0172 mmol, 35%). The compound was analysed by ^{1}H-NMR.

^{1}H-NMR (key peaks) L^2 = 2.96 (1H, d, *J* 15.0, -C*H*H-C_6H_4-CHH-), 2.82 (1H, d, *J* 15.0, -CHH-C_6H_4-C*H*H-), 2.65 (1H, d, *J* 15.0, -CHH-C_6H_4-CH*H*-), 2.58 (1H, d, *J* 15.0, CH*H*-C_6H_4-CHH-); L^3 = Ph

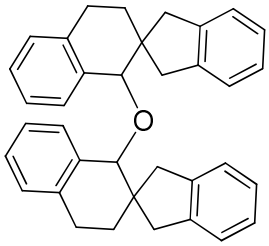
Mosher's ester of racemic 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol (369b).

The compound was prepared similarly as described for the Mosher's ester of (*R*) 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol.

^{1}H-NMR (key peaks) L^3 = 3.10 (1H, d, *J* 18.0, -C*H*H-C_6H_4-CHH-), 2.87 (1H, d, *J* 15.0, -CHH-C_6H_4-C*H*H-), 2.75 (1H, d, *J* 15.0, -CHH-C_6H_4-CH*H*-), 2.69 (1H, d, *J* 15.0, CH*H*-C_6H_4-CHH-); L^2 = Ph

The relative positions of the L^2 and L^3 peaks indicate that the *R*-alcohol was formed predominantly (Figure and Table in Appendix 5.2).[245] The ^{1}H-NMR spectra are shown in Appendix 5.2.7.

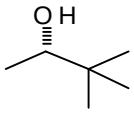
Attempted synthesis of (1S)-(+)-10 camphorsulfonyl ester derivative of 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol 18 (367); resulted in formation of ether linked product (368):



To a solution of 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol **363a** (50 mg, 0.200 mmol) in dry DCM (4 mL) was added TEA (0.055 mL, 0.400 mmol, 2.0 eq) and DMAP (0.5 mg, 0.02 eq). To the solution was added (*S*)-(+)-10-camphorsulfonyl chloride (0.075 g, 0.300 mmol, 1.5 eq) at 0 ^{o}C. The resulting solution was stirred at 21-22 ^{o}C for overnight. The completion of the reaction was checked by TLC. The reaction mixture was diluted with water (10 mL) followed by extraction with DCM (2 x 10 mL). The combined organic layers were washed with 1 M HCl (2 x 10 mL), sat. $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator to give an oil. The oil was purified by flash column chromatography using hexane:EtOAc (90:10) to give a product as a colourless oil (0.028 g, 0.058 mmol, 58%). The oil converted into a solid on standing. The solid was recrystallised from n-pentane: diethyl ether to give crystals for X-ray analysis. δ_H (300 MHz, $CDCl_3$) 7.24-7.18 (6H, m, 6 -CH of -C_6H_4-), 7.08-7.98 (8H, m, 8-CH of -C_6H_4-), 6.88-6.68 (2H, m, 2-CH of -C_6H_4-), 4.17 (2H, s, -C*H*O-), 3.02-2.83 (4H, m, 2 x -CH_2-C_6H_4),

2.60-2.33 (8H, d, 2 x -C*H*$_2$-C_6H_4-C*H*$_2$-), 2.32-2.22 (2H, m, 2 x-C_6H_4-CH_2-C*H*H-), 1.63-1.52 (2H, m, 2 x-C_6H_4-CH_2-CH*H*-); The X-ray Structure was obtained (more details in Appendix 5.1.6).

(*S*)-3,3-Dimethylbutan-3-ol.



This compound is known and fully characterized.[272]

A mixture of catalyst (1*R*,2*R*) 3C-tethered-Ru complex **181** (6.2 mg, 0.010 mmol, 1 mol%) in FA:TEA (5:2) (0.500 mL) was stirred at 28 ^oC under an inert atmosphere in a Schlenk tube. To this, 3,3-dimethylbutan-3-one (0.100 g, 1.00 mmol) was added and stirred at 30 ^oC for 24 h under an inert atmosphere. The completion of the reaction was checked by TLC. The reaction mixture was filtered through a short column of silica using hexane:EtOAc (1:1). The filtrate was concentrated to give a crude alcohol (0.100 g). The crude compound was purified by flash column chromatography to give 3,3-dimethylbutan-3-ol as a colourless oil (0.055 g, 0.539 mmol, 56%). $[\alpha]_D^{22}$ = +2.1 (*c* 0.750 in $CHCl_3$) [lit. value $[\alpha]_D$ = +31.0 (*c* 1.0 in $CHCl_3$) 60% ee (*S*)][272]; δ_H (300 MHz, $CDCl_3$) 3.51-3.43 (1H, m, -C*H*OH-), 1.40 (1H, d, *J* 4.0, -CHO*H*-), 1.12 (3H, d, *J* 6.0, -CHOH-C*H*$_3$), 0.89 (9H, s, -C(C*H*$_3$)$_3$); δc (75 MHz, $CDCl_3$) 75.63, 34.87, 25.38(3C), 17.86; the enantiomeric excess was determined by Chiral GC (Chrompak CP-Chirasil Dex Cβ Column, Oven temperature 70 ^oC, Injection temperature 220 ^oC, Detection temperature 220 ^oC, Gas Helium, Pressure 15 psi) R_t (min) = 19.513 min (minor enantiomer *R*), 20.237 min (major enantiomer *S*), %ee = 10% (*S*). The spectroscopic data were in agreement with literature values. [272]

4 References

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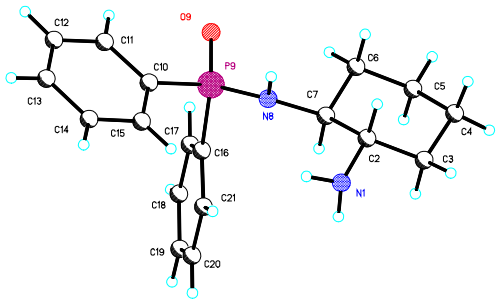
5 Appendix

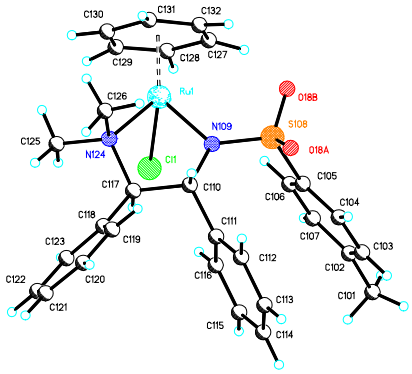
5.1 X-ray data

5.1.1 X-ray crystallography data of (1*S*,2*S*)-*N*-(diphenylphosphinyl)-1,2-diaminocyclohexane 260.



X-ray data for **sc1**; Crystal Data: $C_{18}H_{23}N_2OP$, M = 314.35, Orthorhombic, space group P2(1)2(1)2(1), a = 6.75579(17), b = 15.9177(5), c = 16.3083(6) A, α = 90 deg., β = 90 deg., γ = 90 deg., U = 1753.74(9) A^3 (by least squares refinement on 4475 reflection positions), T = 296(2)K, λ = 0.71073 A, Z = 4, D(cal) = 1.191 Mg/m^3, F(000) = 672. mu(MoK-α) = 0.160 mm^-1. Crystal character: colourless block. Crystal dimensions 0.40 x 0.12 x 0.08 mm.

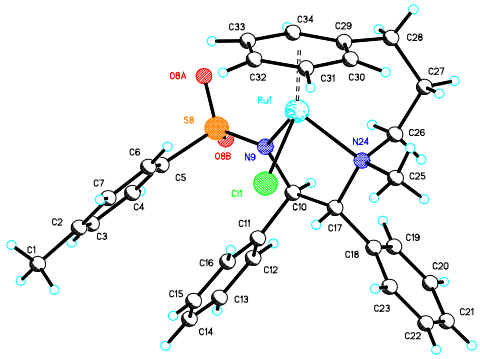
5.1.2 X-ray crystallography data of *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzeneruthenium chloride 299.



X ray data for **rs3**; CCDC no. 793889, *Crystal Data:* $C_{31}H_{37}ClN_2O_3RuS$, M = 654.21, Triclinic, space group P1 a = 10.3603(2), b = 11.0519(3), c = 14.0747(3) A, α = 90.6376(19) deg., β = 103.5283(17) deg., γ = 107.614(2) deg., U = 1487.56(6) A^3 (by least squares refinement on 22067 reflection positions), T = 100(2)K, λ =

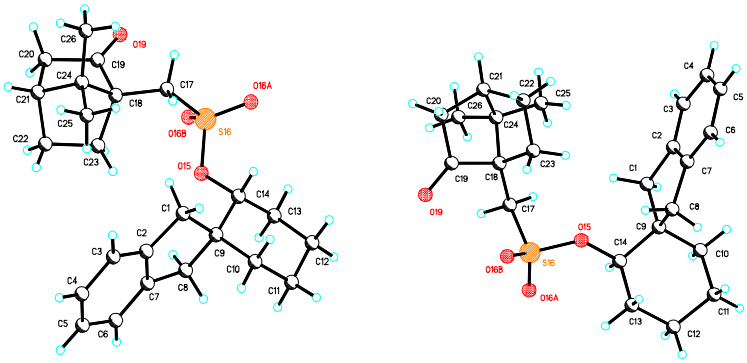
0.71073 A, Z = 2, D(cal) = 1.461 Mg/m^3, F(000) = 676. mu(MoK-α) = 0.721 mm^-1. Crystal character: orange block. Crystal dimensions 0.40 x 0.18 x 0.14 mm.

5.1.3 X-ray crystallography data of {*N*-[(1*R*,2*R*)-1,2-diphenylethyl-2-3-(3-phenylpropyl)(methylamino)]-4-methylbenzenesulfonamide}ruthenium chloride monomer 302.



X-ray data for **rs4**; CCDC no. 793888, *Crystal Data:* $C_{31}H_{33}ClN_2O_2RuS$, M = 634.17, Orthorhombic, space group P2(1)2(1)2(1) a = 8.39707(8), b = 9.14896(9), c = 35.0858(3) A, α = 90 deg., β = 90 deg., γ = 90 deg., U = 2695.44(4) A^3 (by least squares refinement on 7176 reflection positions), T = 100(2)K, λ = 1.54184 A, Z = 4, D(cal) = 1.563 Mg/m^3, F(000) = 1304. mu(MoK-α) = 6.436 mm^-1. Crystal character: orange block. Crystal dimensions 0.2108 x 0.1391 x 0.0319 mm.

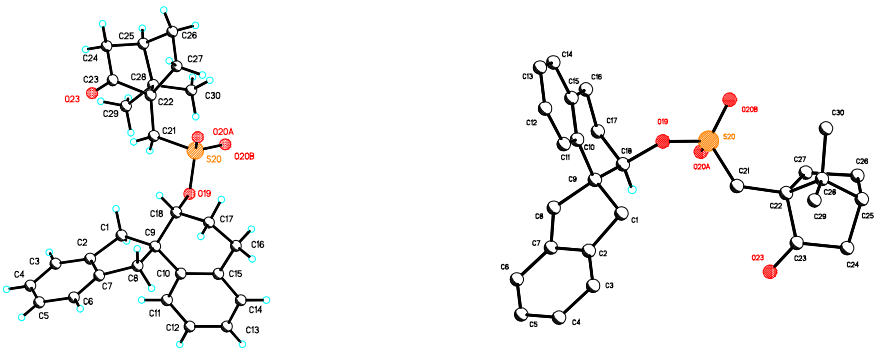
5.1.4 X-ray crystallography data of (1*S*)-(+)-10 camphorsulfonyl ester derivative of 1',3'-dihydro-2H-spiro[cyclohexane-1,2'-inden]-2-ol 332.



X-ray crystallographic data for (*R*)-**12 ('RS5')**; CCDC no. 817152, *Crystal Data:* $C_{24}H_{32}O_4S$, M = 416.56, Monoclinic, space group P2(1), a = 9.9752(2), b =

10.52392(16), c = 11.2107(2) Å , α = 90˚, β = 116.107(3)˚, γ = 90˚, U = 1056.81(3) $Å^3$ (by least squares refinement on 14569 reflection positions), T = 100(2) K, λ = 0.71073 Å, Z = 2, D(cal) = 1.309 Mg/m^3, F(000) = 448. mu(MoK-α) = 0.181 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.50 x 0.30 x 0.30 mm.

5.1.5 X-ray crystallography data of (1*S*)-(+)-10-camphorsulfonyl ester derivative of 1,3,3',4'-tetrahydro-spiro[2H-indene-1,2'-[2H]-naphthalene]-2'-ol 366.

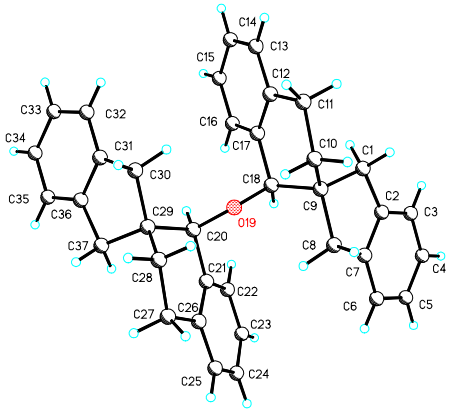


X-ray crystalographic data for (R)-7 **('RS7')**; CCDC no. 817154, *Crystal Data:* $C_{28}H_{32}O_4S$, M = 464.60, Orthorhombic, space group P2(1)2(1)2(1), a = 7.43712(9), b = 8.62914(9), c = 36.4793(4) Å, α = 90˚, β = 90˚, γ = 90˚, U = 2341.09(5) $Å^3$ (by least squares refinement on 26920 reflection positions), T = 100(2) K, λ = 1.54184 Å, Z = 4, D(cal) = 1.318 Mg/m^3, F(000) = 992. mu(MoK-α) = 1.491 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.20 x 0.16 x 0.08 mm.

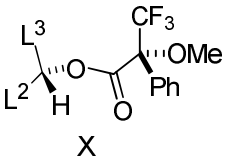
5.1.6 X-ray crystallography data of ether linked product 368:

Attempted synthesis of (1S)-(+)-10 camphorsulfonyl ester derivative of 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol 367.

X-ray crystallographic data: **(RS6-dimer)**; CCDC no. 817153, *Crystal Data:* $C_{36}H_{34}O$, M = 482.63, Monoclinic, space group P2(1)/n, 10.3318(3), b = 18.3947(5), c = 14.2896(4) Å, α = 90˚, β = 108.039(3)˚, γ = 90˚, U = 2582.24(12) $Å^3$ (by least squares refinement on 13397 reflection positions), T = 100(2) K, λ = 1.54184 Å, Z = 4, D(cal) = 1.241 Mg/m^3, F(000) = 1032. mu(MoK-α) = 0.552 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.30 x 0.20 x 0.12 mm. Note that as this molecule is in the centrosymmetric space group P2(1)/n, it must be racemic; the space group contains two *RR*- and two *SS*- configuration molecules.



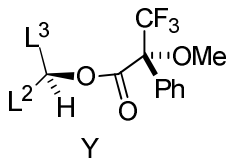
5.2 Data for Mosher's esters



X

(*R*,*R*) Mosher's ester

Mosher's ester derived from alcohol obtained using (*R*,*R*) **181**



Y

(*S*,*R*) Mosher's ester

Mosher's ester derived from alcohol obtained using (*S*,*S*) **181** or racemic alcohol

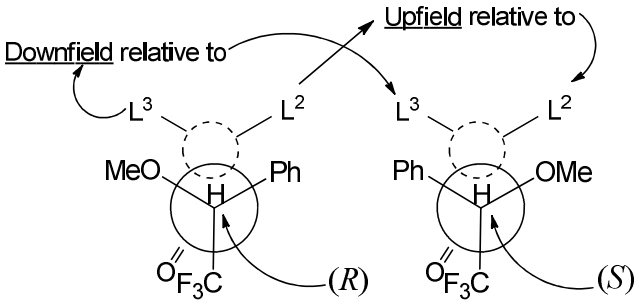
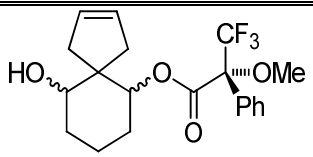
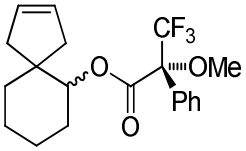
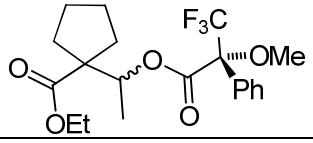
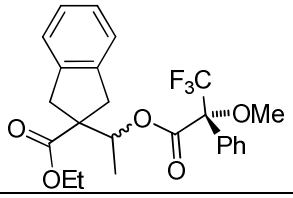
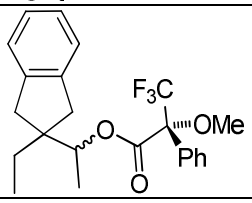
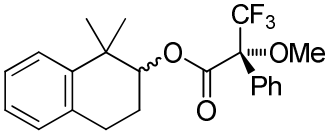
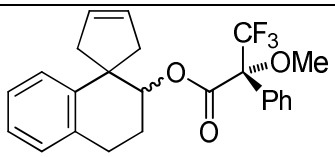
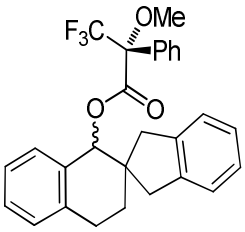
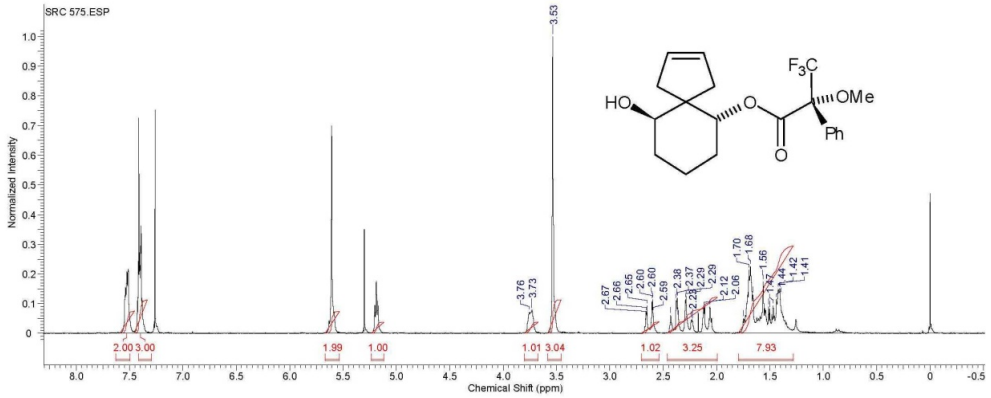


Figure: Mosher's ester derivatives and configuration correlation model.[245]

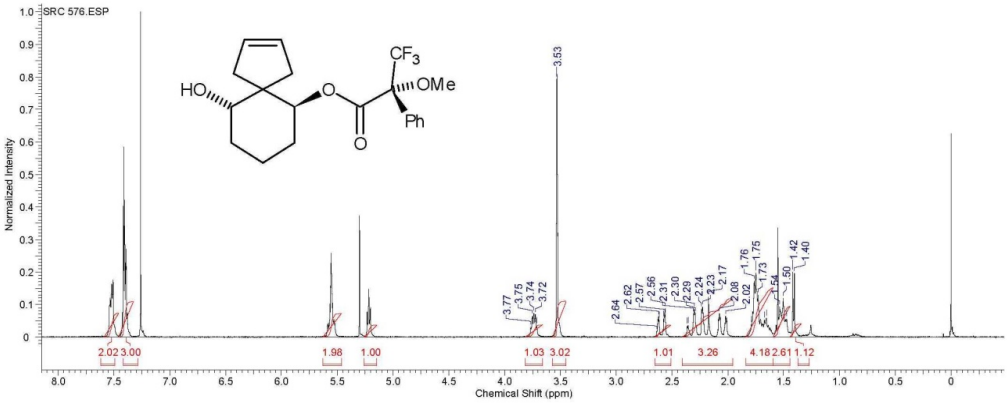
Table : NMR chemical shift differences for diastereomeric Mosher's esters.[245]

Compd	Mosher's esters	L^3	L^2	δ (X-Y) L^3	δ (X-Y) L^2
330		-C*H*$_2$- CH=CH- C*H*$_2$-	-C*H*$_2$-	+0.03 +0.05 +0.04	-0.04
331		-C*H*$_2$- CH=CH- C*H*$_2$-	-C*H*$_2$-	+0.07 +0.06 +0.04 +0.06	-0.08
345		-(C*H*$_2$)$_4$-	-C*H*$_3$	+0.03	-0.07
346		-C*H*$_2$- C$_6$H$_4$-C*H*$_2$- -	-C*H*$_3$	+0.04 +0.05 +0.04 +0.04	-0.10
347		-C*H*$_2$- C$_6$H$_4$-C*H*$_2$- -	-C*H*$_3$	+0.02 +0.08 +0.04 +0.05	-0.06
364		-(C*H*$_3$)$_2$	-C*H*$_2$-	+0.06 +0.07	-0.04
365		-CH$_2$- CH=CH- C*H*$_2$-	-C*H*$_2$-	+0.12	-0.06
369		-C$_6$H$_4$-	-C*H*$_2$- C$_6$H$_4$- C*H*$_2$-	-	-0.15 -0.05 -0.10 -0.11

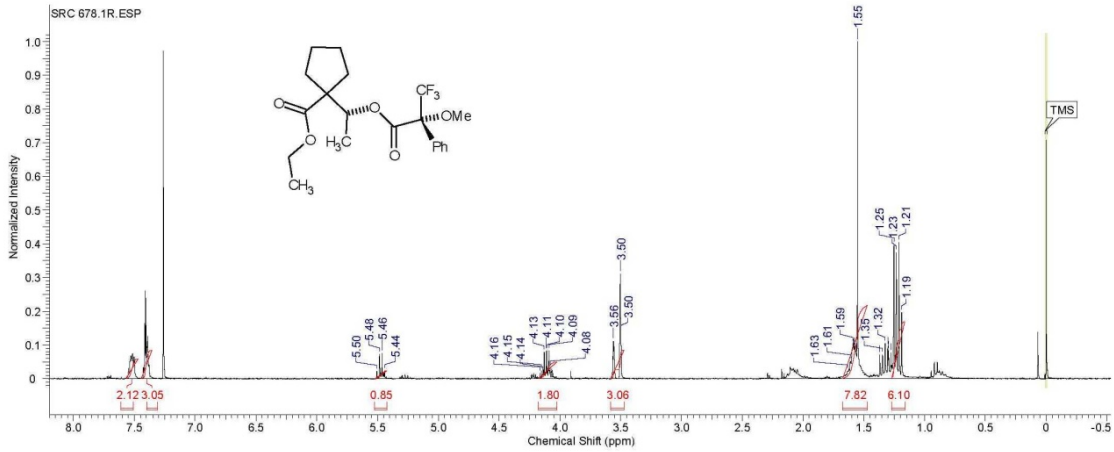
5.2.1 ^{1}H-NMR of Mosher's monoester of (*R*,*R*) spiro[4,5]dec-2-ene-6,10-diol (**330a)**.



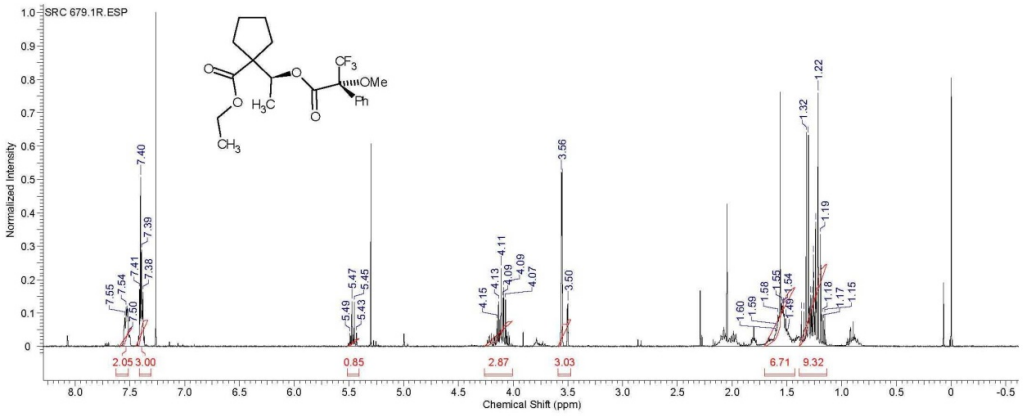
^{1}H-NMR of Mosher's monoester of (*S*,*S*) spiro[4,5]dec-2-ene-6,10-diol (**330b**).



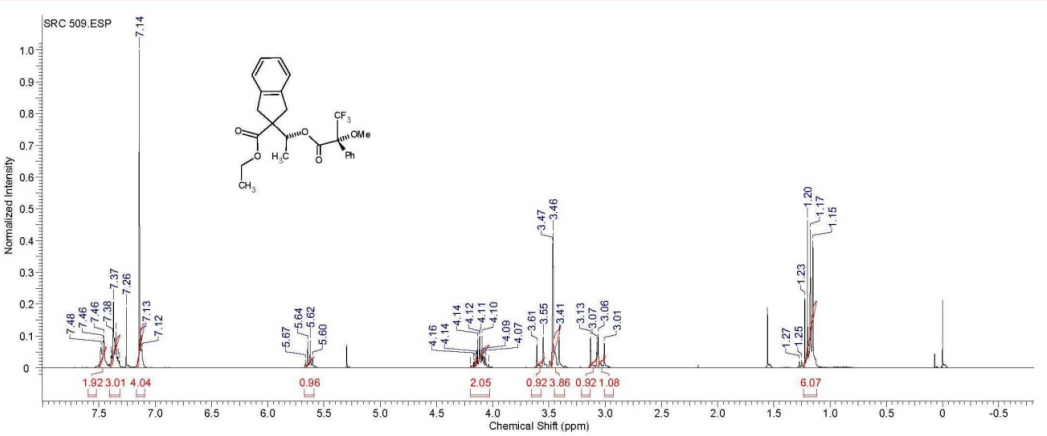
5.2.2 ^{1}H-NMR of Mosher's ester of ethyl (*R*)1-(1-hydroxyethyl)cyclopentanecarboxylate (**345a**).



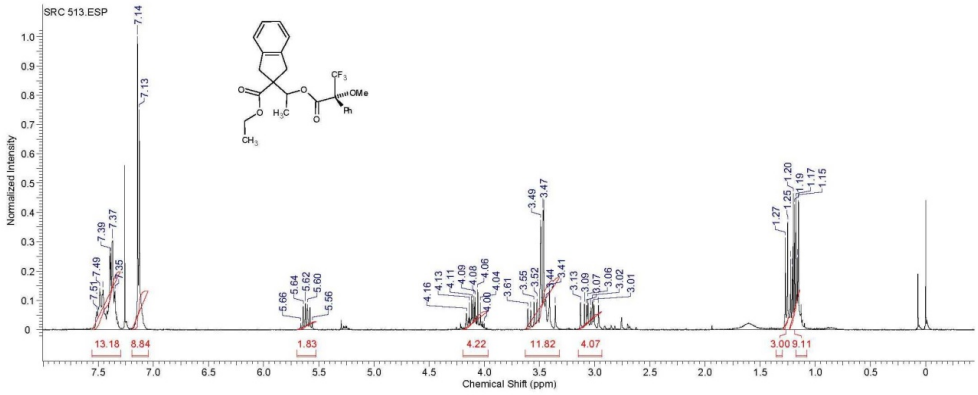
^{1}H-NMR of Mosher's ester of ethyl (*S*)1-(1-hydroxyethyl)cyclopentanecarboxylate (**345b**).



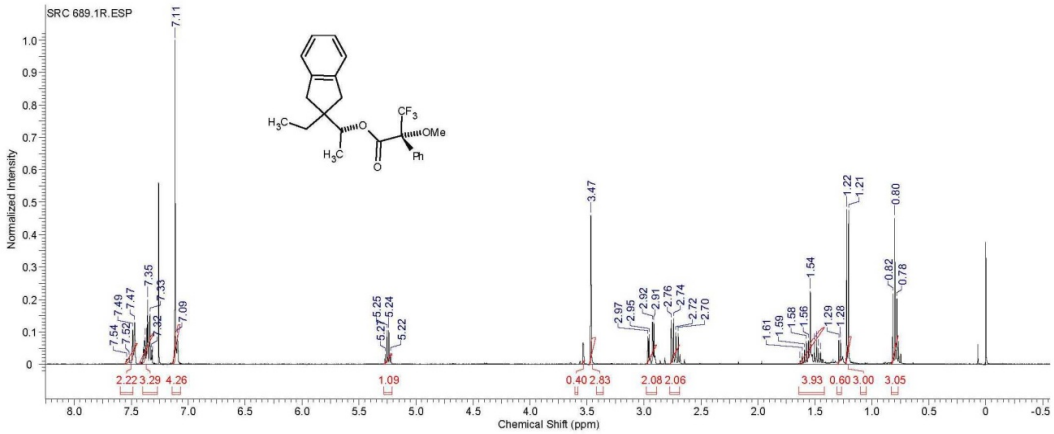
5.2.3 ^{1}H-NMR of Mosher's ester of ethyl (*R*)-2-(1-hydroxyethyl)-2,3-dihydro-1H-indene-2-carboxylate (**346a**).



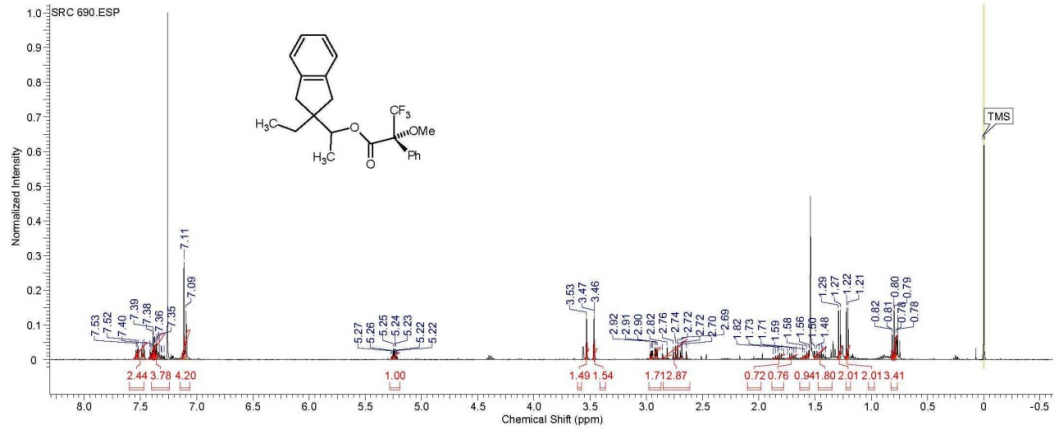
^{1}H-NMR of Mosher's ester of racemic ethyl 2-(1-hydroxyethyl)-2,3-dihydro-1H-indene-2-carboxylate (**346b**).



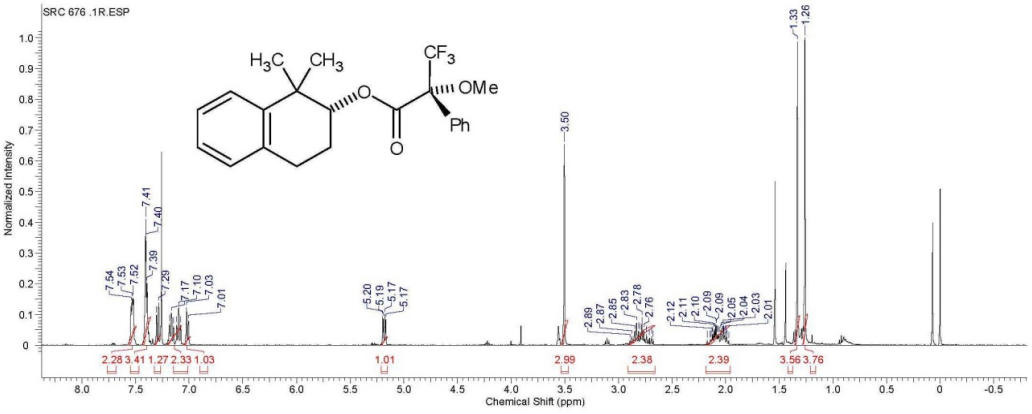
5.2.4 ^{1}H-NMR of Mosher's ester of (*R*)1-(2-ethyl-2,3-dihydro-1H-indene-2-yl)ethanol **347a**.



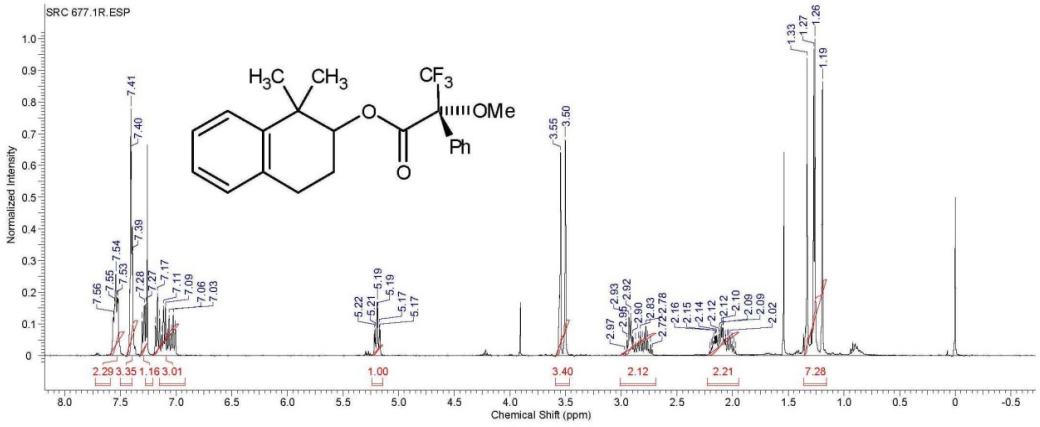
^{1}H-NMR of Mosher's ester of racemic 1-(2-ethyl-2,3-dihydro-1H-indene-2-yl)ethanol **347b**.



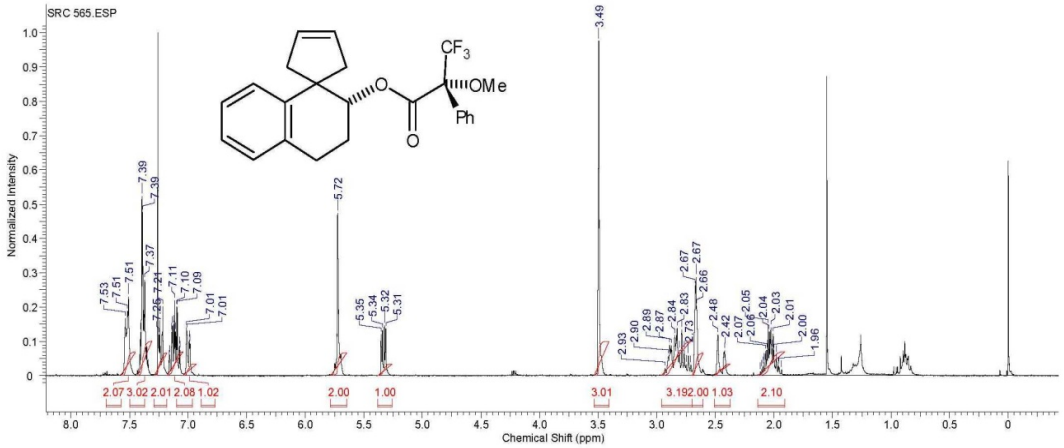
5.2.5 ^{1}H-NMR of Mosher's ester of (*R*) 1,1-dimethyl-3,4-dihydronaphthalen-2-ol **364a**.



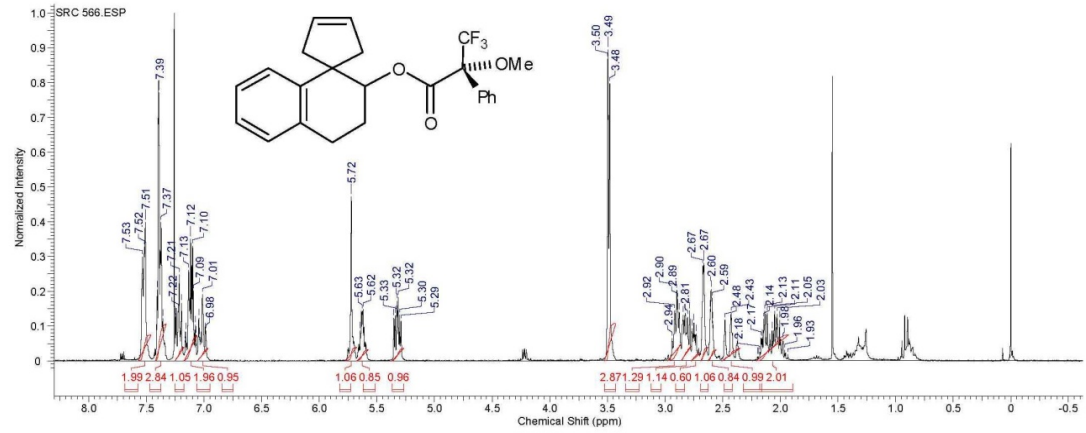
^{1}H-NMR of Mosher's ester of racemic 1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol **364b**.



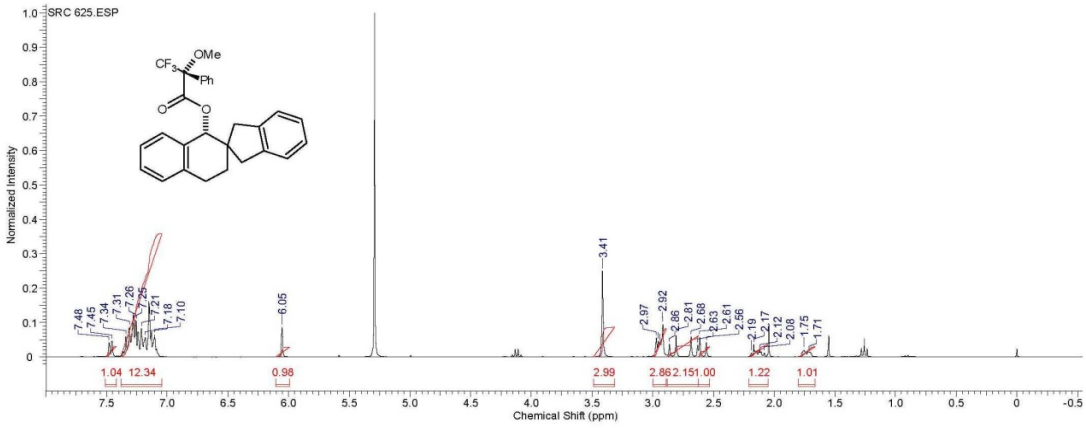
5.2.6 ^{1}H-NMR of Mosher's ester of (*R*) 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol **365a**.



^{1}H-NMR of Mosher's ester of racemic 3',4'-dihydro-2'H-spiro[cyclopent-3-ene-1,1'-naphthalene]-2'-ol **365b**.



5.2.7 ^{1}H-NMR of Mosher's ester of (*R*) 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol **369a**.



^{1}H-NMR of Mosher's ester of 1,3,3',4'-tetrahydro-spiro[2H-indene-2,2'-[2H]-naphthalene]-1'-ol **369b**.